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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 487/04, 495/04, 491/04, A61K 31/50, 31/40, 31/38, 31/34, 31/415

A1

(11) International Publication Number: **WO 99/29695**

(43) International Publication Date: 17 June 1999 (17.06.99)

(21) International Application Number: PCT/SE98/02191

(22) International Filing Date: 1 December 1998 (01.12.98)

(30) Priority Data:

9704542–1	5 December 1997 (05.12.97)	SE
9801989–6	4 June 1998 (04.06.98)	SE

(71) Applicant *(for all designated States except MG US)*: ASTRA PHARMACEUTICALS LTD. [GB/GB]; Home Park, Kings Langley, Herts WD4 8DH (GB).

(71) Applicant *(for MG only)*: ASTRA AKTIEBOLAG [SE/SE]; S–151 85 Södertälje (SE).

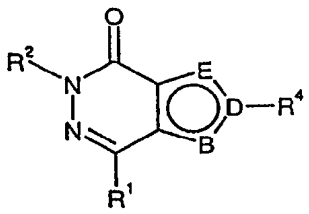
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BANTICK, John [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). COOPER, Martin [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). THORNE, Philip [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). PERRY, Matthew [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB).

(74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S–151 85 Södertälje (SE).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL COMPOUNDS



(I)

(57) Abstract

The invention provides certain pyrrolo–, thieno–, furano– and pyrazolo–[3,4–*d*]–pyridazinones of general formula (I), processes for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and methods of treatment involving their use.

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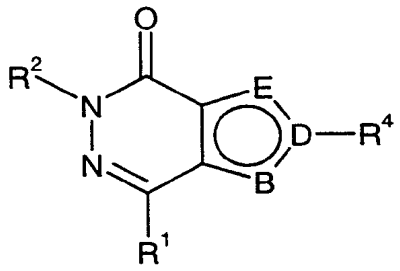
NOVEL COMPOUNDS

The present invention relates to certain pyrrolo-, thieno-, furano-and pyrazolo-[3,4-*d*]pyridazinones, processes for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and methods of treatment involving their use.

In accordance with the present invention, there is provided a compound of the general formula



(I)

wherein B represents a group CH or a nitrogen (N), sulfur (S) or oxygen (O) atom; D represents a carbon (C) or nitrogen (N) atom; E represents a group CR^3 or a nitrogen (N) atom; when D is a carbon atom, then B is a sulfur or oxygen atom and E is a group CR^3, and when D is a nitrogen atom, then either B is a group CH and E is a group CR^3 or a nitrogen atom, or B is a nitrogen atom and E is a group CR^3; R^1 represents a group NR'R'' where R' represent a hydrogen atom or a C_1-C_6 alkyl group, R'' represents a C_1-C_6 alkyl group, or R' and R'' together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated heterocyclic ring, or R^1 represents a C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3-alkyloxyC_1-C_3-alkyl, C_3-C_6-cycloalkyloxyC_1-C_3-alkyl, C_3-C_6 alkenyl, phenyl, C_3-C_7 cycloalkyl, C_3-C_5 cycloalkylmethyl or C_3-C_7 cycloalkenyl group, each of which may be optionally substituted by one or more halogen atoms; R^2 represents a methyl group, or a C_2-C_6 alkyl group optionally substituted by a C_1-C_6 alkoxy group other than in the 1-position; R^3 represents a hydrogen atom or a group X-R^5 or X-Ar^1; X represents a group -O-, $S(O)_n$, $SO_2N(R^6)$ or $C(=O)N(R^6)$; n is 0, 1 or 2; R^5 represents an optionally substituted alkyl or alkenyl group, or, additionally, in the case where X represents $SO_2N(R^6)$ or $C(=O)N(R^6)$, R^5 and R^6 together with the nitrogen atom to which they are

attached may form an optionally substituted 3- to 7-membered heterocyclic ring; Ar^1 represents an optionally substituted phenyl or pyridyl group; R^6 represents a hydrogen atom, C_1-C_6 alkyl or is linked to R^5 as defined above; R^4 represents a group CHR^7Ar^2 or Ar^3 or, additionally, in the case where D represents a carbon atom, a group $C(O)Ar^2$ or $CR^7(OH)Ar^2$; Ar^2 represents an aryl or heteroaryl group which may be optionally substituted; Ar^3 represents an acenaphthenyl, indanyl or fluorenyl group, each of which may be optionally substituted; and R^7 represents a hydrogen atom or a C_1-C_4 alkyl group; or a pharmaceutically-acceptable salt or solvate thereof.

In the present specification, unless otherwise indicated, an alkyl or alkenyl substituent or an alkyl moiety in an alkoxy, alkoxycarbonyl, (di)alkylamino, acylamino, alkylsulfonamido, alkylamido or (di)alkylsulfamoyl substituent group may be linear or branched. Furthermore, the alkyl moieties in a dialkylamino or dialkylsulfamoyl substituent group may be the same or different.

R^1 represents a group NR'R'' where R' represent a hydrogen atom or a C_1-C_6 alkyl, preferably C_1-C_4 alkyl, group, R'' represents a C_1-C_6 alkyl, preferably C_1-C_4 alkyl, group, or R' and R'' together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated heterocyclic ring, or R^1 represents a C_1-C_6, preferably C_3-C_5, alkyl group (e.g. propyl, isopropyl, butyl or isobutyl), a C_1-C_6 alkoxy group (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentoxy or hexoxy), C_1-C_3-alkyloxyC_1-C_3-alkyl (e.g. $-CH_2-O-CH_3$), C_3-C_6-cycloalkyloxyC_1-C_3-alkyl (e.g. $-CH_2$-O-cyclopropyl, $-CH_2$-O-cyclobutyl or $-CH_2$-O-cyclopentyl), a C_3-C_6 alkenyl group (e.g. propenyl or butenyl), a phenyl group, a C_3-C_7, preferably C_3-C_5, cycloalkyl group (e.g. cyclopropyl, cyclobutyl or cyclopentyl), a C_3-C_5 cycloalkylmethyl group (e.g. cyclopropylmethyl, cyclobutylmethyl or cyclopentylmethyl), or a C_3-C_7, preferably C_3-C_5, cycloalkenyl group (e.g. cyclopropenyl, cyclobutenyl or cyclopentenyl, each of which may be optionally substituted by one or more, preferably one to four, e.g. one or two, halogen atoms (e.g. fluorine or chlorine). Where R^1 groups contain a double bond the first carbon atom of the R^1 group cannot be part of the olefin.

R^2 represents a methyl group, or a C_2-C_6, preferably C_2-C_4, alkyl group optionally substituted by a C_1-C_6, preferably C_1-C_4, alkoxy group (e.g. methoxy, ethoxy, propoxy,

isopropoxy, butoxy or isobutoxy) other than in the 1-position. Thus, the alkoxy substituent, if present, is attached to a carbon atom other than the carbon atom which is directly bonded to the ring nitrogen atom.

R^3 represents a hydrogen atom or a group X-R^5 or X-Ar^1.

X represents a group -O-, $S(O)_n$ where n is 0, 1 or 2 or a group $SO_2N(R^6)$ or $C(=O)NR^6$. Preferably X represents a group -O-, $S(O)_n$ where n is 0, 1 or 2, or a group $C(=O)NR^6$.

The group R^5 represents an optionally substituted alkyl or alkenyl group, or, additionally, in the case where X represents $SO_2N(R^6)$ or $C(=O)N(R^6)$, R^5 and R^6 together with the nitrogen atom to which they are attached may form an optionally substituted 3- to 7-membered heterocyclic ring. If R^5 represents an optionally substituted alkyl group, the alkyl group will preferably contain from 2 to 10, particularly from 2 to 6, carbon atoms or if R^5 represents an optionally substituted alkenyl group, the alkenyl group will preferably contain from 3 to 10, particularly from 3 to 6, carbon atoms. R^5 groups cannot form enamines or enol ethers. The alkyl or alkenyl group or heterocyclic ring may be substituted preferably by one or more, e.g. one, two, three or four, substituents independently selected from amido, amino, carboxyl, cyano, hydroxyl, C_1-C_6 alkoxy (preferably C_1-C_4 alkoxy), C_1-C_6 alkylthio (preferably C_1-C_4 alkylthio), C_1-C_6 alkylcarbonyl (preferably C_1-C_4 alkylcarbonyl), C_1-C_6 alkoxycarbonyl (preferably C_1-C_4 alkoxycarbonyl), C_3-C_7 cycloalkyl (preferably C_5-C_6 cycloalkyl), (di) C_1-C_6 alkylamino (preferably (di)methylamino or (di)ethylamino), C_2-C_6 acylamino (preferably C_2-C_4 acylamino), C_1-C_6 alkylsulfonamido (preferably C_1-C_4 alkylsulfonamido), tetrahydrofuranyl, dioxolanyl, imidazolyl, haloC_1-C_6alkylsulfonamido and tetrazolyl. Especially preferred substituent groups are hydroxyl, carboxyl, methoxy, methylthio, methylcarbonyl, cyclopentyl, -$NHC(O)CH_3$, tetrahydrofuranyl, dioxolanyl and imidazolyl groups.

Ar^1 represents an optionally substituted phenyl or pyridyl group. The phenyl or pyridyl group may be substituted preferably by one or more, e.g. one to four, substituents independently selected from carboxyl, hydroxyl, C_2-C_6, preferably C_2-C_4, acylamino, C_1-C_6, preferably C_1-C_4, alkylamido, C_1-C_6, preferably C_1-C_4, alkylsulfonamido and

(di)C_1-C_6, preferably C_1-C_4, alkylsulfamoyl. The group Ar^1 is preferably a pyridyl, particularly 2-pyridyl, group.

R^4 represents a group CHR^7Ar^2 or Ar^3 or, additionally, in the case where D represents a carbon atom, a group $C(O)Ar^2$ or $CR^7(OH)Ar^2$. R^4 is preferably a group CHR^7Ar^2, $C(O)Ar^2$ or $CR^7(OH)Ar^2$.

R^7 represents a C_1-C_4 alkyl group (e.g. methyl or ethyl) or, most preferably, a hydrogen atom.

Ar^2 represents an aryl or heteroaryl group which may be optionally substituted. Examples of suitable aryl and heteroaryl groups include phenyl, naphthyl, pyridyl , quinolinyl, isoquinolinyl, naphthyridinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, thienyl, benzothienyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl, indolyl, indolizinyl, pyrazolyl, indazyl, imidazolyl, benzimidazolyl, imidazopyridyl, triazolyl, benzotriazolyl and triazolopyridyl.

The Ar^2 group may be optionally substituted by one or more, preferably one to four, especially one to three, substituent groups independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), trifluoromethyl, trifluoromethoxy, amino, cyano, carboxyl, nitro, C_1-C_6, preferably C_1-C_4, alkyl, C_1-C_6, preferably C_1-C_4, alkoxy, (di)C_1-C_6, preferably C_1-C_4, alkylamino, C_2-C_6, preferably C_2-C_4, acylamino, C_1-C_6, preferably C_1-C_4, alkylsulfonamido, CONH-(C_1-C_6, preferably C_1-C_4, alkyl), and C_1-C_6, preferably C_1-C_4, alkoxycarbonyl.

Ar^2 is preferably a phenyl, naphthyl, pyridyl, quinolinyl or imidazopyridyl group which may be optionally substituted by one to three substituents independently selected from halogen, cyano, trifluoromethyl and C_1-C_6 alkoxy (especially methoxy).

Ar^3 represents an acenaphthenyl, indanyl or fluorenyl group, each of which may be optionally substituted by one or more, e.g. one to four, substituent groups. The optional substituents may be the same as those for Ar^2.

Preferred compounds of the invention include:

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one,

2,6-Dihydro-2-(2-methoxyethyl)-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one,

2,6-Dihydro-7-[(3-hydroxypropyl)thio]-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one,

4-{[2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1-oxo-1*H*-pyrrolo[3,4-*d*]pyridazin-7-yl]thio}butanoic acid,

2,6-Dihydro-7-[(3-hydroxypropyl)sulfinyl]-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one,

2,6-Dihydro-7-[(3-hydroxypropyl)sulfonyl]-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one,

2-[1-Hydroxy-1-(1-naphthalenyl)methyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-*d*]pyridazin-4(5*H*)-one,

5-Methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)thieno[2,3-*d*]pyridazin-4(5*H*)-one,

3-[(3-Hydroxypropyl)thio]-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-thieno[2,3-*d*]pyridazin-4(5*H*)-one,

5-Methyl-7-(2-methylpropyl)-2-(1-naphthalenylcarbonyl)thieno[2,3-d]pyridazin-4(5H)-one,

3-[(3-Hydroxypropyl)sulfinyl]-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenyl-methyl)thieno[2,3-d]pyridazin-4(5H)-one,

4-{[4,5-Dihydro-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4-oxothieno[2,3-d]pyridazin-3-yl]thio}butanoic acid,

5-Methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-3-(2-pyridinylthio)thieno[2,3-d]pyridazin-4(5H)-one,

3-[(3-Hydroxypropyl)sulfonyl]-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenyl-methyl)thieno[2,3-d]pyridazin-4(5H)-one,

2-[1-Hydroxy-1-phenylmethyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one,

5-Methyl-7-(2-methylpropyl)-2-phenylmethylthieno[2,3-d]pyridazin-4(5H)-one,

3-[(3-Hydroxypropyl)thio]-5-methyl-7-(2-methylpropyl)-2-phenylmethylthieno[2,3-d]pyridazin-4(5H)-one,

3-[(3-Hydroxypropyl)sulfonyl]-5-methyl-7-(2-methylpropyl)-2-phenylmethylthieno-[2,3-d]pyridazin-4(5H)-one,

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-phenylmethyl-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-phenylmethyl-7-(2-pyridinylthio)-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-7-[(3-hydroxypropyl)thio]-2-methyl-4-(2-methylpropyl)-6-phenylmethyl-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(3,4,5-trimethoxyphenyl)methyl-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-2-methyl-6-(1-naphthalenylmethyl)-4-(1-methylethyl)amino-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(4-pyridinyl)methyl-1H-pyrrolo[3,4-d]pyridazin-1-one,

6-(2-Chlorophenyl)methyl-2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one,

6-(3,5-Difluorophenyl)methyl-2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one,

6-(2-Chloro-6-fluorophenyl)methyl-2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one,

6-(3-Chloro-2-fluorophenyl)methyl-2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(2-quinolinylmethyl)-1H-pyrrolo[3,4-d]-pyridazin-1-one,

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(2-trifluoromethylphenyl)methyl-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-6-(2-imidazo[1,2-a]pyridinyl)methyl-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-N-[3-(1-1H-imidazolyl)propyl]-2-methyl-4-(2-methylpropyl)-1-oxo-6-phenylmethyl-1H-pyrrolo[3,4-d]pyridazin-1-one-5-carboxamide,

2,5-Dihydro-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4H-pyrazolo[3,4-d]pyridazin-4-one,

2,6-Dihydro-6-methyl-4-(2-methylpropyl)-2-(1-naphthalenylmethyl)-7H-pyrazolo[3,4-d]pyridazin-7-one,

2,5-Dihydro-3-[(3-hydoxypropyl)thio]-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4H-pyrazolo[3,4-d]pyridazin-4-one,

2-[1-Hydroxy-1-(1-naphthalenyl)methyl]-5-methyl-7-(2-methylpropyl)furo[2,3-d]pyridazin-4(5H)one,

5-Methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)furo[2,3-d]pyridazin-4(5H)one,

2-[1-Hydroxy-1-(3-cyanophenyl)methyl]-5-methyl-7-(2-methylpropyl)furo[2,3-d]pyridazin-4(5H)one,

2-(3-Cyanophenyl)methyl-5-methyl-7-(2-methylpropyl)furo[2,3-d]pyridazin-4(5H)one,

2-(2-Trifluoromethylphenyl)methyl-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one,

2-[(1-Hydroxy-1-pyridin-3-yl)methyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one hydrochloride,

5-Methyl-7-(2-methylpropyl)-2-(3-pyridinylmethyl)thieno[2,3-d]pyridazin-4(5H)-one,

2-(2-Chloro-6-fluorophenyl)methyl-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one,

2-[(1-Hydroxy-1-quinolin-3-yl)methyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one,

5-Methyl-7-(2-methylpropyl)-2-(3-quinolinylmethyl)thieno[2,3-d]pyridazin-4(5H)-one hydrochloride,

2-(3-Chlorophenyl)methyl-3-(2-hydroxyethoxy)-7-(methoxymethyl)-5-methylthieno[2,3-d]pyridazin-4(5H)-one,

2-[(3-Chlorophenyl)methyl]-7-cyclohexyl-3-(2-hydroxyethoxy)-5-methylthieno[2,3-d]pyridazin-4(5H)-one,

2-[(3-Chlorophenyl)methyl]-3-(2-hydroxyethoxy)-5-methyl-7-phenylthieno[2,3-d]pyridazin-4(5H)-one,

2-[(3-Chlorophenyl)methyl]-7-cyclopentyl-3-(2-hydroxyethoxy)-5-methylthieno[2,3-d]pyridazin-4(5H)-one,

7-Cyclopropylmethyl-3-methoxy-5-methyl-2-[(3-trifluoromethylphenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one,

7-Cyclopropylmethyl-5-methyl-3-[2-(methylthio)ethoxy]-2-[(3-trifluoromethylphenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one,

7-Cyclopropylmethyl-3-(2-methoxyethoxy)-5-methyl-2-[(3-trifluoromethyl-phenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one,

3-Cyclopentylmethoxy-7-cyclopropylmethyl-5-methyl-2-[(3-trifluoromethyl-phenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one,

7-Cyclopropylmethyl-5-methyl-3-(tetrahydrofuran-2-ylmethoxy)-2-[(3-trifluoromethylphenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one,

7-Cyclopropylmethyl-3-(3-hydroxy-3-methyl-butoxy)-5-methyl-2-[(3-trifluoromethyl-phenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one,

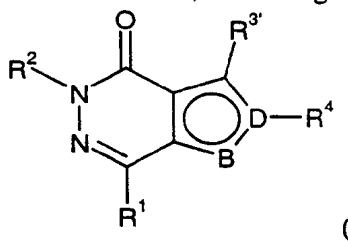
N-{3-[7-Cyclopropylmethyl-5-methyl-4-oxo-2-[(3-trifluoromethylphenyl)methyl]-4,5-dihydrothieno[2,3-d]pyridazin-3-yl]oxypropyl}acetamide,

7-Cyclopropylmethyl-3-([1,3]dioxolan-4-ylmethoxy)-5-methyl-2-[(3-trifluoromethyl-phenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one, and

7-Cyclopropylmethyl-5-methyl -3-(4-oxopentyl)oxy-2-[(3-trifluoromethyl-phenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one.

The present invention further provides a process for the preparation of a compound of formula (I) as defined above which comprises:

(a) when X represents $S(O)_n$ and n is 1 or 2, oxidising a compound of general formula

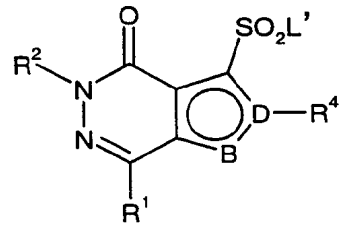


(II)

wherein $R^{3'}$ represents S-R^5 or S-Ar^1 and B, D, R^1, R^2, R^4, R^5 and Ar^1 are as hereinbefore defined, in the presence of an appropriate quantity of a suitable oxidising agent (e.g. 3-chloroperoxybenzoic acid or potassium peroxymonosulfate, commercially sold under the trade mark "OXONE") and an appropriate organic solvent (e.g. dichloromethane) under conditions which are well known to those skilled in the art; or

(b) when X represents $S(O)_n$ and n is 0, reacting a corresponding compound of formula (I) in which E is CR^3 and R^3 is a hydrogen atom, with a compound of general formula (III), R^8-S-S-R^8, wherein the groups R^8 both represent R^5 or Ar^1 as previously defined, or with a compound of general formula (IV), L-S-R^8, wherein L represents a leaving group such as an arylsulfinate group and R^8 is as defined above, in the presence of lithium diisopropylamide (LDA) at a temperature from -78 °C to ambient temperature (20°C); or

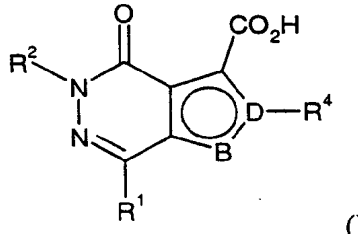
(c) when X represents $SO_2N(R^6)$, reacting a compound of general formula



(V)

wherein L' represents a leaving group such as a halogen atom (e.g. chlorine) and B, D, R^1, R^2 and R^4 are as defined above, with a compound of general formula (VI), HNR^6R^8, wherein R^6 and R^8 are as hereinbefore defined, e.g. in an aqueous solution of sodium hydrogen carbonate; or

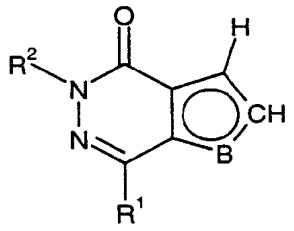
(d) when X represents $C(=O)N(R^6)$, reacting a compound of general formula



(VII)

wherein B, D, R^1, R^2 and R^4 are as hereinbefore defined with a compound of formula (VI) as defined above, in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and 1-hydroxybenzotriazole hydrate in the presence of a solvent such as dimethylformamide; or

(e) when D is a carbon atom, E is CR^3 , R^3 is a hydrogen atom and R^4 is $CH(OH)Ar^2$, reacting a compound of general formula



(VIII)

wherein B, R^1 and R^2 are as hereinbefore defined, with a compound of general formula (IX), Ar^2CHO, where Ar^2 is as hereinbefore defined, in the presence of lithium diisopropylamide at -78°C to ambient temperature (20°C); or

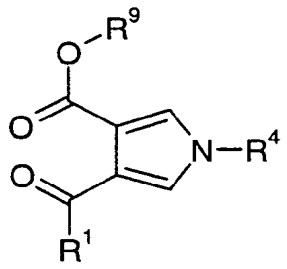
(f) when D is a carbon atom, E is CR^3, R^3 is a hydrogen atom and R^4 is CHR^7Ar^2, reducing a corresponding compound of formula (I) in which R^4 is $CR^7(OH)Ar^2$ (e.g. as prepared in (e) above), in the presence of triethylsilane and trifluoroacetic acid; or

(g) when D is a carbon atom, E is CR^3, R^3 is a hydrogen atom and R^4 is $C(O)Ar^2$, oxidising a corresponding compound of formula (I) in which R^4 is $CH(OH)Ar^2$ as prepared in (e) above, e.g. in the presence of potassium permanganate; or

(h) when D is a carbon atom, E is CR^3, R^3 is a hydrogen atom, R^4 is $CR^7(OH)Ar^2$ and R^7 is a C_1-C_4 alkyl group, reacting a corresponding compound of formula (I) in which R^4 is $C(O)Ar^2$ as prepared in (g) above, with a C_1-C_4 alkylating agent, e.g. a Grignard reagent such as a C_1-C_4 alkylmagnesium halide, in the presence of a solvent, e.g. tetrahydrofuran; or

(i) when D is a carbon atom, E is CR^3, R^3 is a hydrogen atom and R^4 is Ar^3, reacting a compound of formula (VIII) as hereinbefore defined, with 1-indanone, 2-indanone, 9-fluoreneone or 1-acenaphthenone, in the presence of lithium diisopropylamide and optionally cerium (III) chloride at -78°C to ambient temperature (20°C), followed by a reduction reaction, e.g. in the presence of triethysilane and trifluoroacetic acid; or

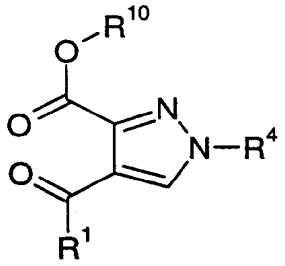
(j) when D is a nitrogen atom, B is CH, E is CR^3 and R^3 is a hydrogen atom, reacting a compound of general formula



(X)

wherein R^9 is an alkyl group (e.g. C_1-C_6 alkyl such as methyl) and R^1 and R^4 are as previously defined, with a compound of general formula (XI), R^2NHNH_2, wherein R^2 is as previously defined, in the presence of a solvent such as ethanol under reflux conditions; or

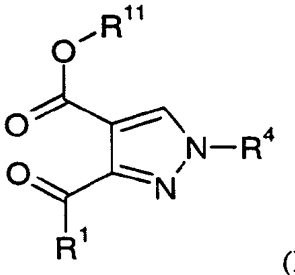
(k) when D is a nitrogen atom, B is CH and E is a nitrogen atom, reacting a compound of general formula



(XII)

wherein R^{10} is an alkyl group (e.g. C_1-C_6 alkyl such as methyl) and R^1 and R^4 are as previously defined, with a compound of formula (XI) as previously defined, in the presence of a solvent such as ethanol under reflux conditions;

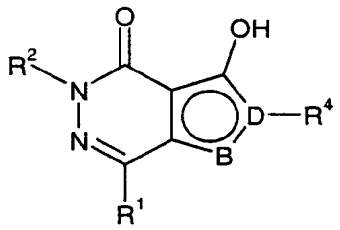
(l) when D is a nitrogen atom, B is a nitrogen atom, E is CR^3 and R^3 is a hydrogen atom, reacting a compound of general formula



(XIII)

wherein R^{11} is an alkyl group (e.g. C_1-C_6 alkyl such as methyl) and R^1 and R^4 are as previously defined, with a compound of formula (XI) as previously defined, in the presence of a solvent such as ethanol under reflux conditions;

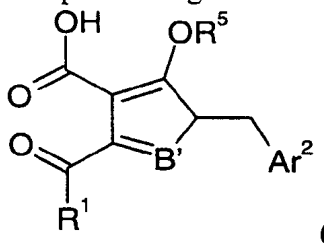
(m) when X is -O-, reacting a compound of general formula



(XIIIA)

wherein B, D, R^1, R^2 and R^4 are as hereinbefore defined, with a compound of general formula (XIIIB), R^8-L'', wherein L'' represents a leaving group such as a halogen atom and R^8 is as defined above; or

(n) when D is a carbon atom, B is a sulfur or oxygen atom, R^3 represents -OR^5 and R^4 represents CH_2Ar^2, reacting a compound of general formula (XIIIC)



(XIIIC)

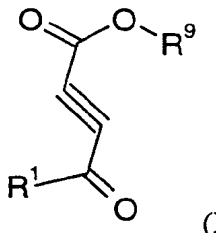
wherein B' represents asulfur or oxygen atom and R^1, R^5 and Ar^2 are as hereinbefore defined, with a compound of formula (XI) as previously defined, in the presence of a solvent such as ethanol under reflux conditions;

and optionally thereafter converting the compound of formula (I) to a further compound of formula (I) and/or forming a pharmaceutically-acceptable salt or solvate of the compound of formula (I).

Compounds of formula (V) may conveniently be prepared by reacting a compound of formula (I) in which E is CR^3 and R^3 is a hydrogen atom, with sulfur dioxide and lithium diisopropylamide at -78°C, followed by reaction with N-chlorosuccinimide in a solvent (e.g. a two-phase solvent system such as water/hydrochloric acid/dichloromethane).

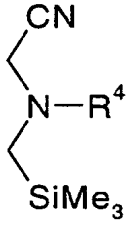
Compounds of formula (VII) may be readily prepared by reacting a compound of formula (I) in which E is CR^3 and R^3 is a hydrogen atom, with carbon dioxide in the presence of lithium diisopropylamide.

Compounds of formula (X) may conveniently be prepared by reacting a compound of general formula



(XIV)

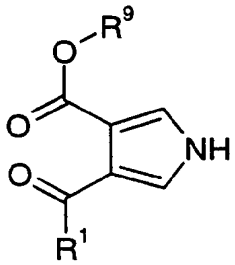
wherein R^1 and R^9 are as defined above, with a compound of general formula



(XV)

wherein R^4 is as hereinbefore defined, in the presence of silver fluoride and a suitable solvent such as acetonitrile.

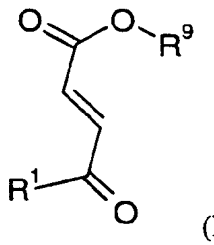
Compounds of formula (X) where R^4 is CH_2Ar^2 can alternatively be prepared from compounds of general formula



(XVI)

where R^1 and R^9 are as previously defined, by reacting with a compound of formula (XVII), Ar^2CH_2L''' where L''' is a leaving group such as halogen and Ar^2 is as defined above. The reaction can be carried out in the presence of a base in a suitable solvent, for example sodium hydride/dimethylformamide (NaH/DMF), optionally in the presence of potassium iodide (KI).

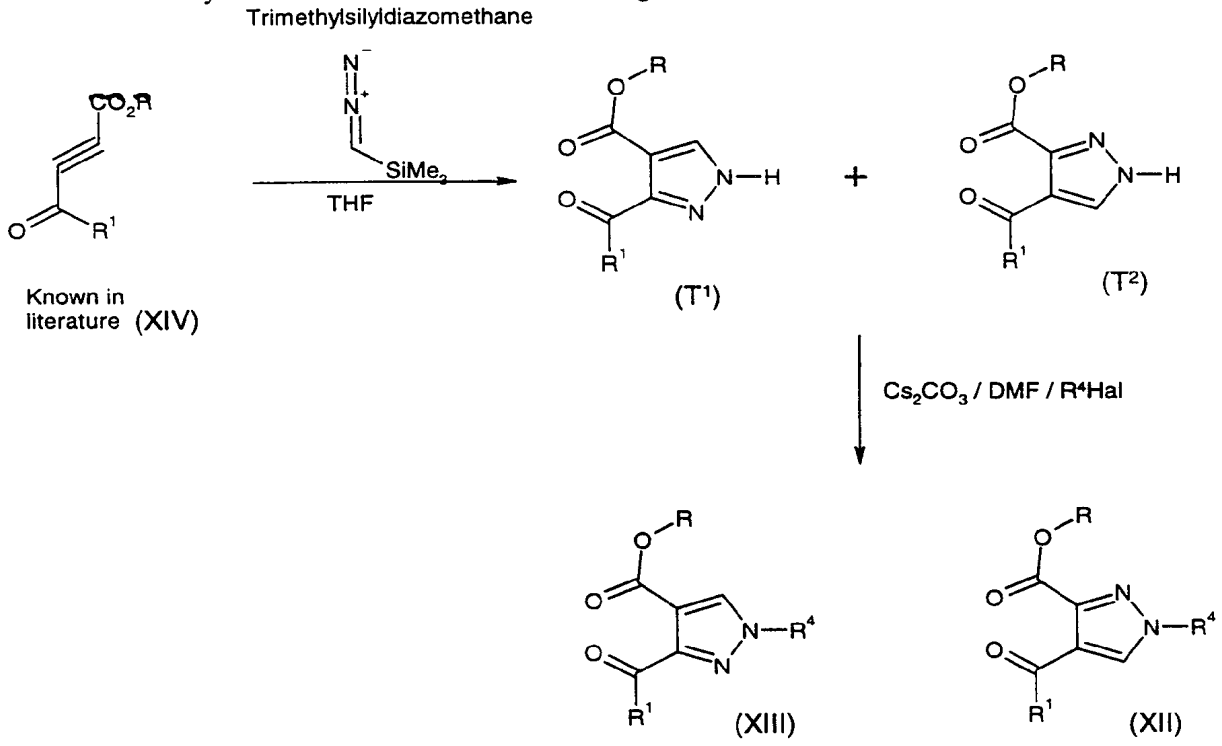
Compounds of formula (XVI) can be prepared by reacting a compound of general formula



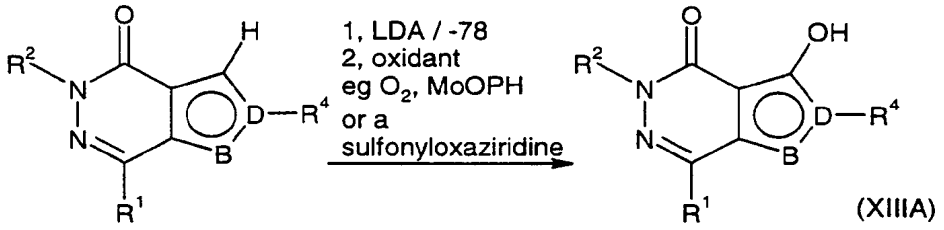
(XVIII)

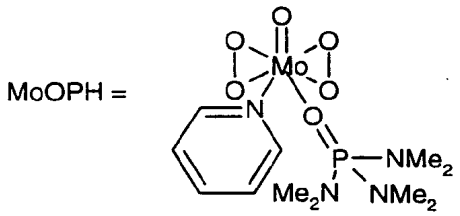
in which R^1 and R^9 are as defined above, with tosylmethyl isocyanide. The reaction is suitably carried out in the presence of a base such as sodium hydride in a solvent mixture such as ether/dimethyl sulfoxide.

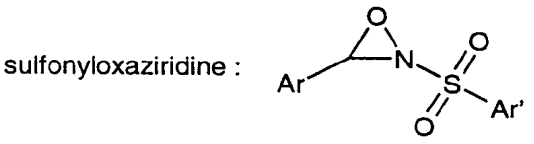
The preparation of compounds of formulae (XII) and (XIII) is described by the following reaction scheme in which $R \equiv R^{10} \equiv R^{11}$, THF denotes tetrahydrofuran, DMF denotes dimethylformamide, Hal denotes a halogen atom and T denotes an intermediate:



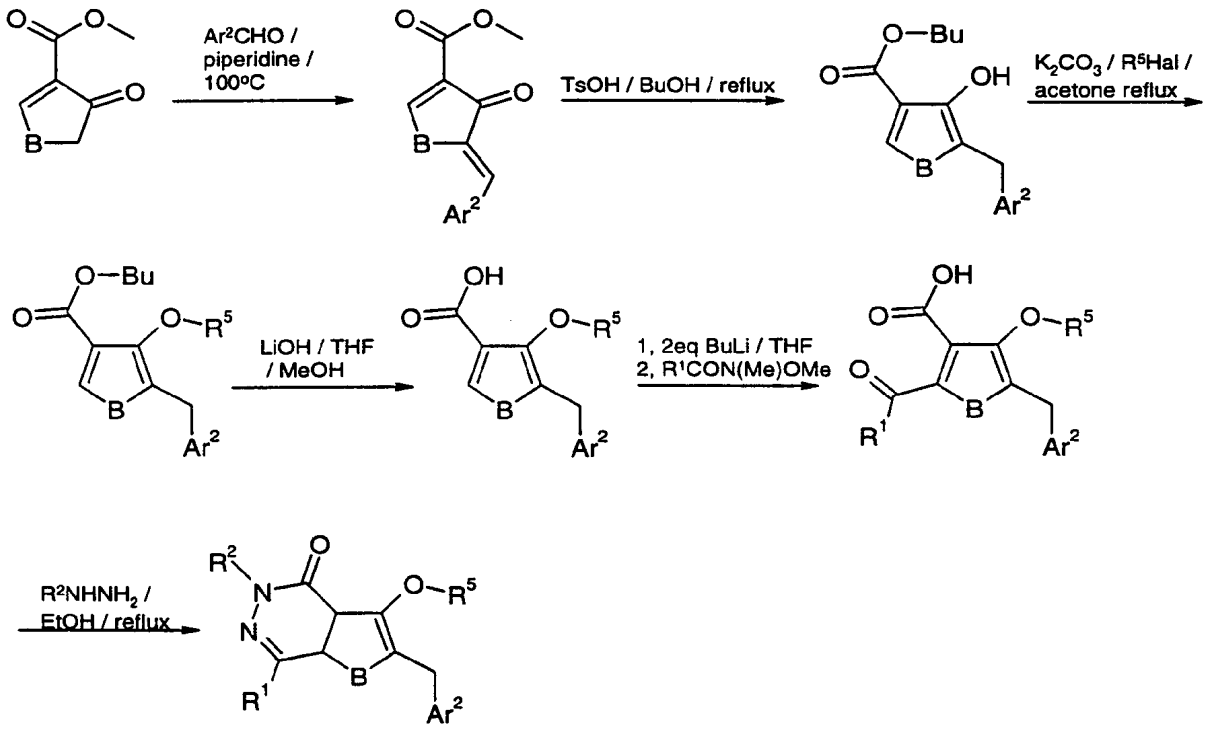
Compounds of formula (XIIIA) can be prepared according to the following reaction scheme:





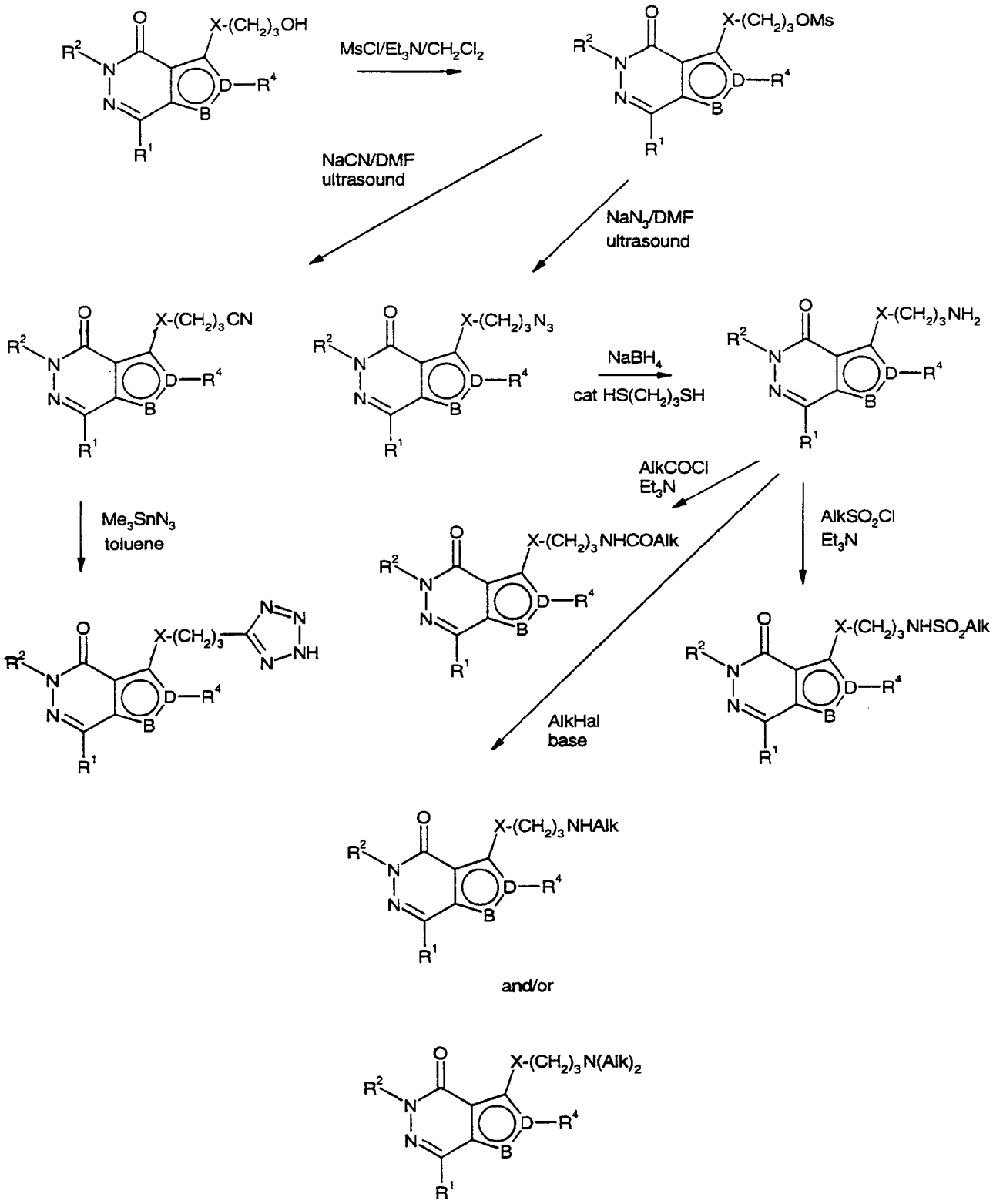


Compounds of formula (XIIIC) can be prepared according to the following reaction scheme:



Compounds of formula (III), (IV), (VI), (VIII), (IX), (XI), (XIIIB), (XIV), (XV) and (XVIII) are either commercially available, are well known in the literature or may be prepared easily using known techniques.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures. For example, compounds of formula (I) where R^5 represents a hydroxy-substituted alkyl group, e.g. $-(CH_2)_3OH$, can be converted to compounds of formula (I) where R^5 represents a cyano-substituted alkyl group, e.g. $-(CH_2)_3CN$, by reaction with methanesulfonyl chloride (MsCl) in the presence of triethylamine and dichloromethane followed by reaction with sodium cyanide in the presence of dimethylformamide. The resulting compounds of formula (I) may in turn be converted into further compounds of formula (I) where R^5 represents a tetrazolyl-substituted alkyl group by reaction with trimethyltin azide (Me_3SnN_3) in toluene under reflux conditions. These and other conversions are shown by way of illustration in the following reaction scheme in which 'Alk' denotes 'alkyl' and 'Hal' denotes 'halogen':


X-(CH2)3OH
MsCl/Et3N/CH2Cl2
X-(CH2)3OMs
NaCN/DMF
ultrasound
NaN3/DMF
ultrasound
X-(CH2)3CN
X-(CH2)3N3
NaBH4
cat HS(CH2)3SH
X-(CH2)3NH2
AlkCOCl
Et3N
Me3SnN3
toluene
AlkSO2Cl
Et3N
X-(CH2)3NHCOAlk
X-(CH2)3NHSO2Alk
AlkHal
base
X-(CH2)3NHAlk
and/or
X-(CH2)3N(Alk)2

It will be appreciated by those skilled in the art that in the process of the present invention certain functional groups such as hydroxyl or amino groups in the intermediate compounds may need to be protected by protecting groups. Thus, the final stage in the preparation of the compounds of formula (I) may involve the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula (I) above may be converted to a pharmaceutically-acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulfonate or *p*-toluenesulfonate, or an alkali metal salt such as a sodium or potassium salt.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The compounds of the invention are useful because they possess pharmacological activity in human and non-human animals. They are therefore indicated as pharmaceuticals for use in the (prophylactic) treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS). Examples of these conditions are:

(1) **(the respiratory tract)** reversible obstructive airways diseases including asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa;

membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata, allergic conjunctivitis and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura;

(6) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease.

The compounds of the invention are also indicated for use as antimicrobial agents, and thus may be used in the treatment of diseases caused by pathogenic micro-organisms.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

The invention further provides a method of effecting immunosuppression which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined to a patient.

The invention still further provides a method of treating, or reducing the risk of, a reversible obstructive airways disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compounds of formula (I) and pharmaceutically-acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically-acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically-acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically-acceptable adjuvant, diluent or carrier.

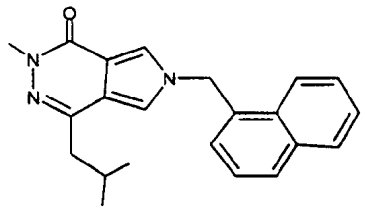
The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically-acceptable adjuvant, diluent or carrier.

The pharmaceutical composition of the invention may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The present invention will be further understood from the following illustrative examples in which, unless otherwise specified, chromatography was carried out over silica and organic solutions were dried over magnesium sulfate. The terms GC, MS, NMR, $CDCl_3$ and DMSO denote respectively gas chromatography, mass spectrometry, nuclear magnetic resonance, chloroform-*d* and dimethyl sulfoxide.

Example 1

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo [3,4-*d*]pyridazin-1-one



a) **(E)-Methyl 6-methyl-4-oxo-2-heptenoate**

To 4-methyl-2-pentanone (25 ml) in stirred dry methanol (120 ml) at -2 °C under nitrogen was added bromine (10.0 ml) in one portion. The temperature of the reaction

mixture rose to about 5 °C. The reaction mixture was stirred at -2 °C for 2 hours until the colour was discharged. Water (100 ml) was added and the mixture was stirred for 16 hours. The reaction mixture was saturated with salt and then extracted with diethyl ether (4 times), which was washed with aqueous sodium hydrogen carbonate solution and then brine. Drying and evaporation gave 1-bromo-4-methyl-2-pentanone as an oil (31 g), contaminated with about 10% of the 3-bromo isomer. GC/MS (EI) 178/180 (M^+)

1-Bromo-4-methyl-2-pentanone (30 g) in toluene (30 ml) was added over 5 minutes to a stirred suspension of methyl (triphenylphosphoranylidene)acetate (112 g) in dry toluene (300 ml) at 90 °C. After 3 hours the thick yellow suspension was cooled and filtered. The filtrate was treated with methyl bromoacetate (16 ml) and the mixture was stirred at 90 °C for 2 hours. On cooling, a precipitate of methoxycarbonylmethyl triphenylphosphonium bromide was filtered off and the filtrate was evaporated to an oil, which was chromatographed with isohexane-dichloromethane (10:1) to afford the sub-title keto ester as an oil (10.2 g).

GC/MS (EI) 170 (M^+), 113 (BP)

^{1}H NMR ($CDCl_3$) : δ 0.95 (d, 6H), 2.18 (m, 1H), 2.50 (d, 2H), 3.81 (s, 3H), 6.66 (d, 1H, *J*=15.9 Hz), 7.06 (d, 1H, *J*=15.9 Hz)

b) <u>Methyl 4-(3-methyl-1-oxobutyl)-1*H*-pyrrole-3-carboxylate</u>

A solution of (E)-methyl 6-methyl-4-oxo-2-heptenoate (10 g) prepared as described in a) above and (*para*-toluenesulfonyl)methyl isocyanide (11.5 g) in a mixture of dry dimethyl sulfoxide (30 ml) and diethyl ether (30 ml) was added over one hour to sodium hydride (2.75 g of a 60% oil dispersion, 0.068 mol) stirred in dry diethyl ether (90 ml) under nitrogen. After a further hour saturated ammonium chloride solution was added and the mixture was extracted with ethyl acetate, which was washed well with water, dried, and evaporated to a gum. The gum was chromatographed with ethyl acetate-isohexane (2:3) to afford a solid (3.3 g) which was crystallised from ethyl acetate-cyclohexane to give the sub-title ester.

Melting point: 136 °C

MS (+ve APCI) $(M+H)^+$ 210

^{1}H NMR ($CDCl_3$) : δ 0.96 (d, 6H), 2.22 (m, 1H), 2.78 (d, 2H), 3.83 (s, 3H), 7.26 (t, 1H), 7.37 (t, 1H), 8.8 (br, 1H)

c) **Methyl 4-(3-methyl-1-oxobutyl)-1-(1-naphthalenylmethyl)-1*H*-pyrrole-3-carboxylate**

To sodium hydride (0.42 g of a 60% oil dispersion, 0.0105 mol), freed from oil, stirred in dry dimethyl formamide (15 ml) under nitrogen was added methyl 4-(3-methyl-1-oxobutyl)-1*H*-pyrrole-3-carboxylate (2.2 g) prepared as described in b) above in portions over 20 minutes. After 10 minutes, potassium iodide (0.01 g) and (1-naphthalenyl)methyl chloride (1.85 g) in dimethyl formamide (20 ml) were added. The mixture was stirred for 4 hours and then poured into 0.5M hydrochloric acid and extracted with ethyl acetate. The organic layer was washed well with water and then brine, dried and evaporated to a gum, which was chromatographed with ethyl acetate-isohexane (1:3) to give an oil. The oil was crystallised from cyclohexane to yield the sub-title pyrrole (2.6g).

Melting point: 81-82 °C

MS (APCI) 350 $(M+H)^+$

^{1}H NMR ($CDCl_3$) : δ 0.94 (d, 6H), 2.2 (m, 1H), 2.76 (d, 2H), 3.79 (s, 3H), 5.50 (s, 2H), 7.17 (d, 1H, *J*=2.7 Hz), 7.23 (d, 1H, *J*=2.7 Hz), 7.25 (m, 1H), 7.46 (dd, 1H), 7.55 (m, 2H), 7.80 (m, 1H), 7.95 (m, 2H)

d) **2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one**

Methyl 4-(3-methyl-1-oxobutyl)-1-(1-naphthalenylmethyl)-1*H*-pyrrole-3-carboxylate (0.35 g) prepared as described in c) above and methylhydrazine (0.10 ml) in ethanol (15 ml) were heated to reflux for 16 hours. The mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate, which was washed with brine, dried, and evaporated to a gum. The gum was chromatographed with ethyl acetate-isohexane (1:1) to afford a solid which was recrystallised from cyclohexane to give 2,6-dihydro-2-

methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (0.16 g).

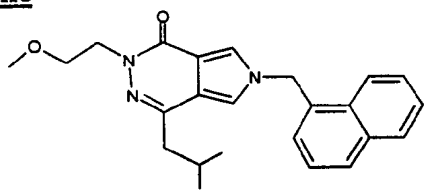
Melting point: 110-112 °C

MS (APCI) 346 $(M+H)^+$

^1H NMR ($CDCl_3$) : δ 0.94 (d, 6H), 2.11 (m, 1H), 2.53 (d, 2H), 3.71 (s, 3H), 5.73 (s, 2H), 7.04 (d, 1H, *J*=2.1 Hz), 7.22 (d, 1H), 7.52 (d, 1H, *J*=2.1 Hz), 7.53 (m, 3H), 7.83 (m, 1H), 7.91 (m, 2H)

Example 2

2,6-Dihydro-2-(2-methoxyethyl)-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one



a) 2,6-Dihydro-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo [3,4-*d*]pyridazin-1-one

Methyl 4-(3-methyl-1-oxobutyl)-1-(1-naphthalenylmethyl)-1*H*-pyrrole-3-carboxylate (0.35 g) prepared as described in Example 1c) above and hydrazine hydrate (0.2 ml) were stirred in ethanol (10 ml) for 2 days. The reaction mixture was poured into water to give a solid which was collected and recrystallised from ethyl acetate-cyclohexane to afford the sub-title pyrrole (0.22 g).

Melting point: 183 °C

MS (APCI) 332 $(M+H)^+$

^1H NMR ($CDCl_3$) : δ 0.95 (d, 6H), 2.11 (m, 1H), 2.53 (d, 2H), 5.75 (s, 2H), 7.10 (d, 1H, *J*=2.1 Hz), 7.26 (m, 1H), 7.52 (d, 1H, *J*=2.1 Hz), 7.52 (m, 3H), 7.82 (m, 1H), 7.92 (m, 2H), 9.08 (br, 1H)

b) 2,6-Dihydro-2-(2-methoxyethyl)-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one

2,6-Dihydro-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo-[3,4-*d*]pyridazin-1-one (0.060 g) prepared in a) above was added in portions to sodium hydride (0.020 g of a 60% oil dispersion, 0.5 mmol), freed from oil, and stirred in dry dimethyl formamide under nitrogen. After 0.5 hour, bromoethyl methyl ether (0.04 ml) was added and the reaction mixture was stirred for 16 hours. The reaction mixture was then poured into 0.5M hydrochloric acid and extracted with ethyl acetate, which was washed with brine, dried, and evaporated to an oil. The oil was chromatographed with ethyl acetate-isohexane (1:1) to give 2,6-dihydro-2-(2-methoxyethyl)-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (0.027 g).

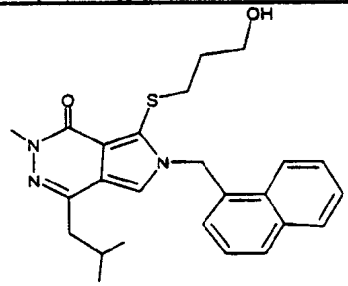
Melting point: 96-98 °C

MS (APCI) 390 $(M+H)^+$

^{1}H NMR ($CDCl_3$) : δ 0.94 (d, 6H), 2.11 (m, 1H), 2.53 (d, 2H), 3.35 (s, 3H), 3.75 (t, 2H), 4.32 (t, 2H), 5.72 (s, 2H), 7.02 (d, 1H, *J*=2.1 Hz), 7.22 (d, 1H), 7.54 (m, 4H), 7.82 (m, 1H), 7.90 (m, 2H)

Example 3

2,6-Dihydro-7-[(3-hydroxypropyl)thio]-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one



To 2,6-dihydro-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyridazin-1-one (0.345 g) prepared as described in Example 1 above and S-{3-[(1,1-dimethylethyl)dimethylsilyl]oxypropyl} *para*toluenethiosulfonate (0.72 g)

(J. Med. Chem., 1995, **38**, 2557) in dry tetrahydrofuran (10 ml) stirred at -78 °C under nitrogen was added lithium diisopropylamide in tetrahydrofuran (0.39M, 5.1 ml). The reaction mixture was allowed to warm to room temperature overnight and then saturated ammonium chloride solution was added. The mixture was extracted with ethyl acetate, which was then washed with brine, dried, and evaporated to a gum. The gum was chromatographed with ethyl acetate-isohexane (1:1) to give the *tert*butyldimethylsilyl ether of the title compound as a solid (0.25 g), MS (APCI) 550 $(M+H)^+$.

To a stirred suspension of this solid (0.25 g) in dry acetonitrile (10 ml) was added 40% hydrofluoric acid (0.07 ml). After 16 hours, aqueous sodium hydrogen carbonate solution was added and the mixture was partially evaporated to leave a residue. The residue was extracted with ethyl acetate, which was washed with brine, dried, and evaporated to a solid. The solid was chromatographed with ethyl acetate-isohexane (3:2) to give, after trituration with diethyl ether-isohexane, 2,6-dihydro-7-[(3-hydroxypropyl)thio]-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (0.17 g).

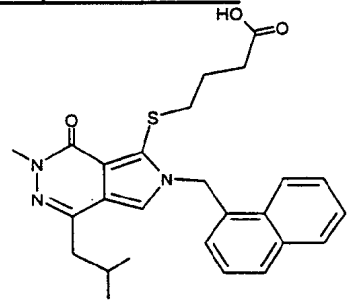
Melting point: 152 °C

MS (APCI) 436 $(M+H)^+$

^{1}H NMR ($CDCl_3$) : δ 0.90 (d, 6H), 1.77 (quint, 2H), 1.98-2.12 (m, 1H), 2.48 (d, 2H), 3.12 (t, 2H), 3.75 (s, 3H), 3.87-4.01 (m, 3H), 5.97 (s, 2H), 6.75 (d, 1H), 7.05 (s, 1H), 7.39 (dd, 1H), 7.53-7.61 (m, 2H), 7.85 (d, 1H), 7.89-7.95 (m, 2H)

Example 4

4-{[2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1-oxo-1*H*-pyrrolo[3,4-*d*]pyridazin-7-yl]thio}butanoic acid



a) **S-{3-[4-methyl-2,6,7-trioxabiclo[2.2.2]octan-1-yl]propyl} *para*toluenethiosulfonate**

To 1-(3-bromopropyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (Tetrahedron Lett. 1983, 24, 5571) (9.4 g) and triethylamine (5 ml) in dry hexamethylphosphoramide (15 ml) was added potassium *para*toluenethiosulfonate (8.5 g) and the mixture was stirred for 3 days. Water was added and the resultant precipitate was filtered off and dissolved in ethyl acetate, which was then washed with water, dried over sodium sulfate, and evaporated to a residue. The residue was triturated with diethyl ether to afford the sub-title ester as a solid (8.0 g).

MS (APCI) 359 $(M+H)^+$

^{1}H NMR (DMSO-d_6) : δ 0.73 (s, 3H), 1.59 (m, 4H), 2.47 (s, 3H), 2.99 (t, 2H), 3.77 (s, 6H), 7.48 (d, 2H), 7.79 (d, 2H)

b) **Methyl 4-{[2,6-dihydro-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1-oxo-1*H*-pyrrolo[3,4-*d*]pyridazin-7-yl]thio}butanoate**

To a stirred solution of 2,6-dihydro-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (0.345 g) prepared as described in Example 1 above and S-{3-[4-methyl-2,6,7-trioxabiclo[2.2.2]octan-1-yl]propyl} *para*toluenethiosulfonate (0.70 g) prepared in a) above in dry tetrahydrofuran (8 ml) at -78 °C under nitrogen was added dropwise lithium diisopropylamide in tetrahydrofuran

(0.39M, 5.1 ml). After one hour, aqueous sodium hydrogen carbonate solution was added and the mixture was extracted with ethyl acetate, which was then washed with brine, dried over sodium sulfate, and evaporated to a gum. The gum was immediately dissolved in methanolic hydrogen chloride solution and after 16 hours the solution was evaporated to leave a residue. The residue was dissolved in ethyl acetate and washed with brine, dried, and evaporated to a gum. Chromatography with ethyl acetate-isohexane (1:3) gave the subtitle ester as a clear oil (0.24 g).

MS (APCI) 478 $(M+H)^+$

^1H NMR ($CDCl_3$), salient peaks: δ 3.10 (t, 2H), 3.62 (s, 3H), 3.75 (s, 3H), 5.95 (s, 2H), 7.02 (s, 1H)

c) **4-{[2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1-oxo-1*H*-pyrrolo[3,4-*d*]pyridazin-7-yl]thio}butanoic acid**

Methyl 4-{[2,6-dihydro-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1-oxo-1*H*-pyrrolo[3,4-*d*]pyridazin-7-yl]thio}butanoate (0.24 g) prepared as described in b) above was stirred with lithium hydroxide hydrate (0.060 g) in tetrahydrofuran-water-methanol (3:1:1) for 3 hours. The solution was evaporated and the resulting residue was partitioned between ethyl acetate and dilute hydrochloric acid. The organic layer was washed with brine, dried, and evaporated to a solid, which was chromatographed with ethyl acetate-isohexane to give, after crystallisation from ethyl acetate-cyclohexane, 4-{[2,6-dihydro-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1-oxo-1*H*-pyrrolo[3,4-*d*]pyridazin-7-yl]thio}butanoic acid (0.075 g).

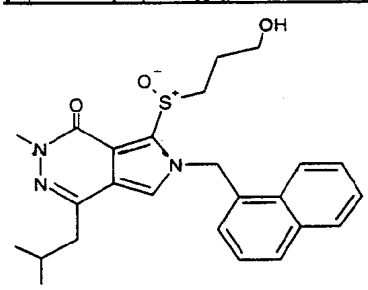
Melting point: 167 °C

MS (APCI) 464 $(M+H)^+$

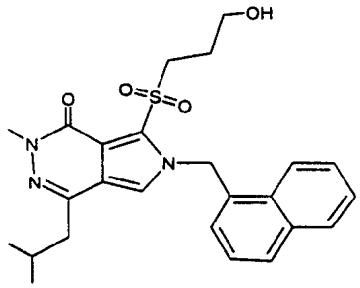
^1H NMR ($CDCl_3$) : δ 0.90 (d, 6H), 1.86 (m, 2H), 2.05 (m, 1H), 2.49 (m, 2H), 2.70 (t, 2H), 2.84 (t, 2H), 3.77 (s, 3H), 6.00 (s, 2H), 6.80 (d, 1H), 7.10 (s, 1H), 7.40 (t, 1H), 7:58 (m, 2H), 7.85-7.94 (m, 3H)

Example 5

2,6-Dihydro-7-[(3-hydroxypropyl)sulfinyl]-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (A) and 2,6-Dihydro-7-[(3-hydroxypropyl)sulfonyl]-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (B)



(A)



(B)

2,6-Dihydro-7-[(3-hydroxypropyl)thio]-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (0.34 g) prepared as described in Example 3 above was dissolved in dichloromethane (7 ml) and 3-chloroperoxybenzoic acid (229 mg) was added. After 4 hours sodium bicarbonate (aqueous) and sodium metabisulfite (aqueous) were added and the mixture was extracted thrice with dichloromethane. The combined organic extracts were washed with brine, dried, filtered and evaporated. The residue was chromatographed eluting with ethyl acetate and then ethyl acetate: ethanol (19:1 - 9:1) to give 2 products. The more polar product was triturated with ether to give 2,6-Dihydro-7-[(3-hydroxypropyl)sulfinyl]-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (A) (48 mg) whilst the less polar product was recrystallised from isohexane-ethyl acetate to give 2,6-dihydro-7-[(3-hydroxypropyl)sulfonyl]-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one (B) (94 mg).

Compound A:

Melting point: 164-166 °C

MS (+ve APCI) $(M+H)^+$ 452

^{1}H NMR (DMSO-d_6) : δ 0.88 (3H, d), 0.89 (3H, d), 1.47-1.65 (2H, m), 1.97-2.10 (1H, m), 2.53 (2H, d), 3.15-3.24 (1H, m), 3.30-3.35 (2H, m), 3.39-3.48 (1H, m), 3.60 (3H, s),

4.56 (1H, t), 6.30 (1H, d), 6.41 (1H, d), 6.73 (1H, d), 7.45 (1H, t), 7.57-7.65 (2H, m), 7.88 (1H, s), 7.91 (1H, d), 7.98-8.02 (1H, m), 8.11-8.14 (1H, m)

Compound B:

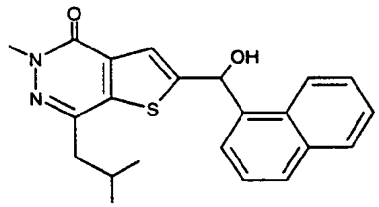
Melting point: 150-151 °C

MS (+ve APCI) $(M+H)^+$ 468

^{1}H NMR (DMSO-d_6) : δ 0.92 (6H, d), 1.57-1.66 (2H, m), 2.10-2.15 (1H, m), 2.60 (2H, d), 3.30-3.36 (2H, m), 3.65 (3H, s), 3.80-3.85 (2H, m), 4.58 (1H, t), 6.35 (1H, d), 6.36 (2H, s), 7.38 (1H, t), 7.58-7.68 (2H, m), 7.86 (1H, d), 8.00 (1H, dd), 8.12 (1H, d), 8.18 (1H, s)

Example 6

2-[1-Hydroxy-1-(1-naphthalenyl)methyl]-5-methyl-7-(2-methylpropyl)thieno [2,3-*d*]pyridazin-4(5*H*)-one



a) **2-(3-Methyl-1-oxobutyl)thiophene-3-carboxylic acid**

Lithium diisopropylamide (86 mmol) in tetrahydrofuran (30 ml) was added at 0 °C to a solution of thiophene-3-carboxylic acid (5 g) in tetrahydrofuran (50 ml). Isovaleraldehyde (4.6 ml) was added as a solution in tetrahydrofuran (30 ml) at 0 °C. The reaction mixture was stirred at 25 °C for 3 hours and then water (100 ml) was added and the tetrahydrofuran was removed *in vacuo*. The aqueous residue obtained was extracted with ethyl acetate and the aqueous phase added to potassium permanganate (12.3 g) and warmed to 60 °C for 1.5 hours. The mixture was filtered, allowed to cool to ambient temperature, and then acidified with dilute hydrochloric acid. The acidic aqueous mixture was extracted with ethyl acetate and the organic extract dried and evaporated to give the sub-title compound as an oil (5.3 g).

MS (APCI) $((M-H^-)^-)$ 211

^{1}H NMR ($CDCl_3$) : δ 1.03 (6H, d), 2.37 (1H, m), 2.95 (2H, d), 7.70 (1H, d), 7.97 (1H, d)

b) **5-Methyl-7-(2-methylpropyl)thieno[2,3-*d*]pyridazin-4(5*H*)-one**

2-(3-Methyl-1-oxobutyl)thiophene-3-carboxylic acid (5.3 g) prepared in a) above was dissolved in ethanol (30 ml) and methylhydrazine (1.5 ml) added. The resultant mixture was heated to reflux for 10 hours. The reaction mixture was evaporated and the residue obtained was dissolved in ethyl acetate. The organic phase was washed twice with dilute hydrochloric acid, twice with saturated sodium hydrogen carbonate solution and once with brine, then dried and evaporated. Purification by chromatography eluting with iso-hexane / ethyl acetate (2:1 to 1:1) gave the sub-title compound as an oil (3.05 g).

MS (APCI) ($(M+H)^+$) 223

^{1}H NMR ($CDCl_3$) : δ 1.00 (6H, d), 2.05 (1H, m), 2.75 (2H, d), 3.85 (3H, s), 7.60 (1H, d), 7.80 (1H, d)

c) **2-[1-Hydroxy-1-(1-naphthalenyl)methyl]-5-methyl-7-(2-methylpropyl)thieno-[2,3-*d*]pyridazin-4(5*H*)-one**

Lithium diisopropylamide (6.75 mmol) in tetrahydrofuran (8 ml) and 1-naphthaldehyde (0.7 ml) in tetrahydrofuran (5 ml) were added alternately to a solution of 5-methyl-7-(2-methylpropyl)thieno[2,3-*d*]pyridazin-4(5*H*)-one (1 g) prepared in b) above in tetrahydrofuran (20 ml) at 0 °C. After 2 hours, water (10 ml) was added, the reaction mixture was acidified with dilute hydrochloric acid and then extracted with ethyl acetate. The organic phase was washed once with dilute hydrochloric acid, twice with saturated sodium hydrogen carbonate solution and once with brine, before being dried and evaporated. Purification by chromatography eluting with isohexane / ethyl acetate (1:1), and subsequent HPLC eluting with the same gave the title compound (0.4 g).

Melting point: 165-7 °C

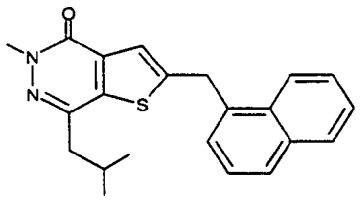
MS (APCI) ($(M+H)^+$) 379

^{1}H NMR (DMSO-d_6) : δ 0.91 (6H, d), 2.12 (1H, m), 2.57 (2H, d), 3.64 (3H, s),

6.77 (1H, d), 6.84 (1H, d), 7.28 (1H, s), 7.48-53 (2H, m), 7.57 (1H, t), 7.79 (1H, d), 7.92 (1H, d), 7.96 (1H, dd), 8.26 (1H, dd)

Example 7

5-Methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)thieno[2,3-*d*] pyridazin-4(5*H*)-one



Triethylsilane (0.3 ml) was added to a solution of 2-[1-hydroxy-1-(1-naphthalenyl)methyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-*d*]pyridazin-4(5*H*)-one (0.3 g) prepared as described in Example 6 above and trifluoroacetic acid (2 ml) in dichloromethane (10 ml). After 30 minutes, the reaction mixture was evaporated and the residue remaining was dissolved in ethyl acetate. The ethyl acetate solution was washed twice with saturated sodium hydrogen carbonate solution and once with brine, and then dried and evaporated. Purification by chromatography eluting with iso-hexane / ethyl acetate (4:1 to 2:1), and subsequent HPLC eluting with isohexane : ethyl acetate (2:1) gave the title compound (0.25 g).

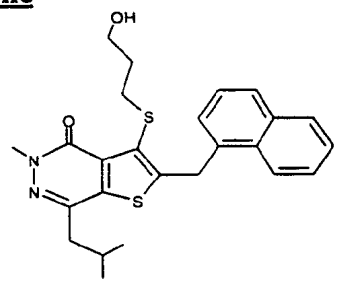
Melting point: 103 °C

MS (APCI) ($(M+H)^+$) 363

^{1}H NMR (DMSO-d_6) : δ 0.86 (6H, d), 2.04 (1H, m), 2.51 (2H, d), 3.65 (3H, s), 4.81 (2H, s), 7.47 (1H, s), 7.48-7.53 (3H, m), 7.60 (1H, d), 7.89 (1H, d), 7.96 (1H, dd), 8.15 (1H, dd)

Example 8

3-[(3-Hydroxypropyl)thio]-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-thieno[2,3-*d*]pyridazin-4(5*H*)-one



Prepared from 5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)thieno[2,3-*d*]-pyridazin-4(5*H*)-one (385 mg) prepared as described in Example 7 above and S-{3-[(1,1-dimethylethyl)dimethylsilyl]oxypropyl} *para*toluenethiosulfonate (600mg) (J. Med. Chem., 1995, **38**, 2557) following the method of Example 3. Yield 370 mg.

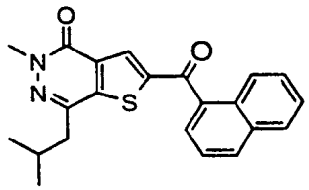
Melting point: 128-130 °C

MS (+ve APCI) $(M+H)^+$ 453

^{1}H NMR (DMSO-d_6) : δ 0.83 (6H, d), 1.67 (2H, quin), 1.93-2.06 (1H, m), 2.46 (2H, d), 3.13 (2H, t), 3.50 (2H, q), 3.70 (3H, s), 4.53 (1H, t), 4.88 (2H, s), 7.45-7.58 (4H, m), 7.90 (1H, d), 7.95-8.04 (2H, m)

Example 9

5-Methyl-7-(2-methylpropyl)-2-(1-naphthalenylcarbonyl)thieno[2,3-d]pyridazin-4(5H)-one



Potassium permanganate (0.335g) and 18-crown-6 (10mg) were added to a solution of 2-[1-hydroxy-1-(1-naphthalenyl)methyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one (example 7, 0.40g) in dichloromethane (30ml) at room temperature. After 1 hour, further potassium permanganate (0.30g) was added and stirring was

continued for a further hour. The mixture was filtered, diluted with dichloromethane (70ml), washed twice with water then with brine, then dried, filtered and evaporated. The residue was purified by column chromatography, eluting with ethyl acetate : isohexane (1:2), to give the title compound (0.14g). This was purified further by preparative normal-phase HPLC with gradient ethyl acetate/isohexane elution.

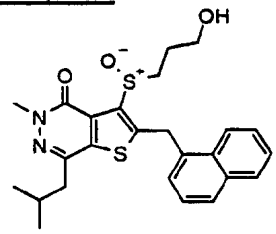
Melting point: 121°C

MS (+ve APCI) 377 ($(M+H)^+$)

^{1}H NMR (DMSO d6) δ 0.98 (6H, d), 2.14-2.26 (1H, m), 2.74 (2H, d), 3.70 (3H, s), 7.60-7.65 (2H, m), 7.70 (1H, dd), 7.79 (1H, s), 7.98 (1H, dd), 8.07-8.11 (2H, m), 8.26 (1H, d).

Example 10

3-[(3-Hydroxypropyl)sulfinyl]-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)thieno[2,3-d]pyridazin-4(5H)-one



3-Chloroperoxybenzoic acid (80%, 0.055g) was added to a stirred solution of 3-{[3-hydroxypropyl]thio}5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)thieno[2,3-d]pyridazin-4(5H)-one (example 8, 0.14g) in dichloromethane (20ml) at room temperature. After 20 hours, the mixture was diluted with dichloromethane (30ml), washed with saturated sodium hydrogen carbonate solution, dried, filtered and evaporated. The residue was purified by column chromatography, eluting with ethyl acetate : isohexane (1:1 then 2:1), followed by preparative normal-phase HPLC with gradient ethyl acetate/isohexane elution to give the title compound (0.05g) as a foam.

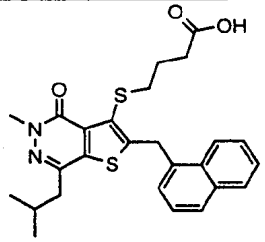
Melting point: 60-65°C

MS (+ve APCI) 469 ($(M+H)^+$)

^{1}H NMR (DMSO d6) δ 0.80 (3H, d), 0.82 (3H, d), 1.81-1.99 (2H, m), 2.03-2.15 (1H, m), 2.44 (2H, d), 3.28-3.39 (2H, m), 3.58 (2H, q), 3.67 (3H, t), 4.65 (1H, t), 4.84 (1H, d), 5.80 (1H, d), 7.51-7.56 (3H, m), 7.61 (1H, d), 7.92 (1H, d), 7.95-7.99 (1H, m), 8.14-8.17 (1H, m).

Example 11

4-{[4,5-Dihydro-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4-oxothieno[2,3-d]pyridazin-3-yl]thio}butanoic acid



a) **4,4,4-Trimethoxybutyl 4-methylbenzenesulfonothioate**

A mixture of *para*-toluenethiosulfonic acid potassium salt (24 mmol), trimethyl 4-bromoorthobutyrate (22 mmol) and hexamethylphosphoramide (30 ml) was stirred at room temperature for 48h and was then poured into 10:1 hexane/diethyl ether (500 ml) and shaken vigorously. The mixture was washed with water (2 x 200 ml) and then brine. The organic phase was collected and dried over $MgSO_4$ and evaporated to yield the sub-title ester as an oil (5.3g) containing *ca* 7% 4,4,4-Trimethoxybutyl 4-methylbenzenesulfonodithioate.

^{1}H NMR ($CDCl_3$) δ 1.95(2H, m), 2.37(2H, t), 2.44(3H, s), 3.02(2H, t), 3.16(9H, s), 7.33(2H, d), 7.80(2H, d).

b) **Methyl 4-{[4,5-dihydro-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4-oxothieno[2,3-d]pyridazin-3-yl]thio}butanoate.**

A solution of lithium diisopropylamide (1.8mmol) in tetrahydrofuran (5ml) was added dropwise to a solution of 5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-

thieno[2,3-d]pyridazin-4(5H)-one (example 7, 0.30g) and 4,4,4-trimethoxybutyl 4-methylbenzenesulfonothioate (0.42g) in tetrahydrofuran (15ml) at -78°C under nitrogen. After 2 hours, the mixture was warmed to room temperature, quenched with 1M hydrochloric acid (25ml) and extracted with ethyl acetate (25ml). The organic extracts were washed with 1M hydrochloric acid, then with sodium hydrogen carbonate solution, then with brine, dried, filtered and evaporated. The residue was purified by column chromatography, eluting with ethyl acetate : isohexane (1:4, 1:2, 1:1 then 1:0), to give the ~~sub-title compound~~ (0.25g) as an oil.

MS (+ve APCI) 495 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 0.88 (6H, d), 2.00 (2H, quin), 1.99-2.11 (1H, m), 2.44 (2H, d), 2.55 (2H, t), 3.20 (2H, t), 3.65 (3H, s), 3.82 (3H, s), 4.87 (2H, s), 7.40-7.50 (4H, m), 7.84 (1H, d), 7.90 (1H, dd), 7.98 (1H, dd).

c) **4-{[4,5-Dihydro-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4-oxothieno[2,3-d]pyridazin-3-yl]thio}butanoic acid**

A solution of lithium hydroxide hydrate (0.035g) in water (1ml) was added to a solution of methyl 4-{[4,5-dihydro-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4-oxothieno[2,3-d]pyridazin-3-yl]thio}butanoate (0.20g) in tetrahydrofuran (6ml) at room temperature. After 2 days, 1M hydrochloric acid (20ml) was added and the mixture was extracted with ethyl acetate (20ml). The organic extracts were washed with brine, dried, filtered and evaporated. The residue was dissolved in ethyl acetate : isohexane (1:2) and the precipitated solid was collected. The solid was suspended in boiling ethyl acetate (20ml), cooled and collected to give the title compound (0.05g).

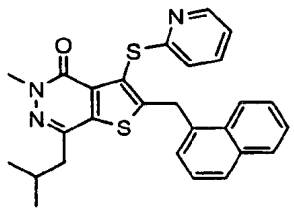
Melting point 154-156°C

MS (+ve APCI) 481 ($(M+H)^+$)

^{1}H NMR (DMSO d6) δ 0.85 (6H, d), 1.76 (2H, quin), 1.94-2.06 (1H, m), 2.38 (2H, t), 2.45 (2H, d), 3.11 (2H, t), 3.69 (3H, s), 4.88 (2H, s), 7.45-7.58 (4H, m), 7.90 (1H, d), 7.97-8.01 (2H, m) 12.09 (1H, brs).

Example 12

5-Methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-3-(2-pyridinylthio)thieno[2,3-d]pyridazin-4(5H)-one



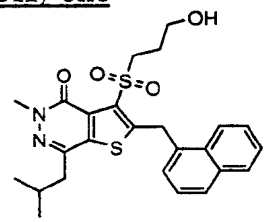
A solution of butyl lithium in hexanes (2.5M, 0.60ml) was added to a solution of diisopropylamine (0.16ml) in tetrahydrofuran (5ml) at 0°C under nitrogen. After 30 minutes, 4ml of the resulting solution was added to a solution of 5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)thieno[2,3-d]pyridazin-4(5H)-one (example 7, 0.207g) and 2,2'-dipyridyl disulfide (0.19g) in tetrahydrofuran (15ml) at -78°C. The mixture was warmed to room temperature, quenched with saturated aqueous ammonium chloride solution (25ml) and extracted with ethyl acetate (50ml). The organic extracts were washed twice with saturated aqueous ammonium chloride solution, twice with saturated sodium hydrogen carbonate solution, then with brine (25ml), dried, filtered and evaporated. The residue was purified by column chromatography, eluting with ethyl acetate : isohexane (1:2 then 1:1), followed by recrystallisation from ethyl acetate/isohexane and then preparative normal-phase HPLC with gradient ethyl acetate/isohexane elution to give the title compound (0.077g) as a foam.

MS (+ve APCI) 472 ($(M+H)^+$)

^{1}H NMR (DMSO d6) δ 0.85 (6H, d), 1.97-2.08 (1H, m), 2.50 (2H, d), 3.59 (3H, s), 4.83 (2H, s), 7.09 (1H, d), 7.14 (1H, dd), 7.35 (1H, td), 7.48-7.52 (3H, m), 7.66 (1H, td), 7.87-7.96 (3H, m), 8.38-8.40 (1H, m).

Example 13

3-[(3-Hydroxypropyl)sulfonyl]-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenyl-methyl)thieno[2,3-d]pyridazin-4(5H)-one



3-Chloroperoxybenzoic acid (80%, 0.27g) was added to a stirred solution of 3-{[3-hydroxypropyl]thio}5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)thieno[2,3-d]pyridazin-4(5H)-one (example 7, 0.28g) in dichloromethane (10ml). After 24 hours, the mixture was diluted with dichloromethane (40ml), washed with saturated sodium hydrogen carbonate solution, dried, filtered and evaporated. The residue was purified by column chromatography, eluting with ethyl acetate : isohexane (1:1 then 2:1 then 1:0), followed by recrystallisation from ethyl acetate/isohexane to give the title compound (0.209g).

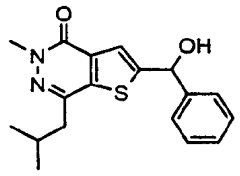
Melting point 160-163°C

MS (+ve APCI) 485 ($(M+H)^+$)

^{1}H NMR (DMSO d6) δ 0.81 (6H, d), 1.87-1.99 (3H, m), 2.45 (2H, d), 3.50 (2H, q), 3.71 (3H, s), 3.96-4.05 (2H, m), 4.70 (1H, t), 5.23 (2H, s), 7.51-7.58 (4H, m), 7.94-8.02 (3H, m).

Example 14

2-[1-Hydroxy-1-phenylmethyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one



A solution of lithium diisopropylamide (13.6mmol) in tetrahydrofuran/hexane (2:1, 22ml) was added dropwise to a solution of 5-methyl-7-(2-methylpropyl)thieno[2,3-

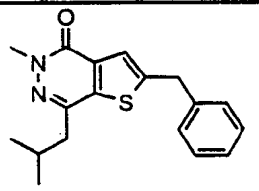
d]pyridazin-4(5H)-one (example 6 step b, 2.00g) in tetrahydrofuran (24ml) at -70°C under nitrogen. Benzaldehyde (2.00ml) was added and after 15 minutes, the mixture was warmed to room temperature. 1M Hydrochloric acid (50ml) was added and the mixture was extracted with ethyl acetate (100ml). The organic extracts were washed twice with 1M hydrochloric acid, twice with saturated sodium hydrogen carbonate solution, then with brine, dried, filtered and evaporated. The residue was purified by column chromatography, eluting with ethyl acetate : isohexane (1:3 then 1:2 then 1:1), to give the title compound (2.48g) of which 0.5g was purified by preparative normal-phase HPLC with gradient ethanol/dichloromethane elution to gave the title compound (0.38g) as an oil.

MS (+ve APCI) 329 ($(M+H)^+$)

^{1}H NMR (DMSO d6) δ 0.92 (6H, d), 2.06-2.18 (1H, m), 2.60 (2H, d), 3.67 (3H, s), 6.11 (1H, d), 6.71 (1H, d), 7.28 (1H, t), 7.36 (1H, s), 7.39 (2H, t), 7.49 (2H, d).

Example 15

5-Methyl-7-(2-methylpropyl)-2-phenylmethylthieno[2,3-d]pyridazin-4(5H)-one



Triethylsilane (1.0ml) was added to a stirred solution of 2-[1-hydroxy-1-phenylmethyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one (example 14, 1.44g) in trifluoroacetic acid (2ml) and dichloromethane (10ml) at room temperature. After 24 hours, saturated sodium hydrogen carbonate solution (100ml) was added and the mixture was extracted with ethyl acetate (100ml). The organic extracts were washed twice with saturated sodium hydrogen carbonate solution, then with brine, and then dried, filtered and evaporated. The residue was purified by column chromatography, eluting with ethyl acetate : isohexane (1:4 then 1:3), to give the title compound (1.11g) as a solid.

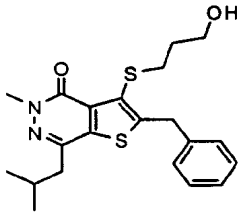
Melting point: 97-98°C

MS (+ve APCI) 313 ($(M+H)^+$)

^{1}H NMR (DMSO d6) δ 0.90 (6H, d), 2.04-2.16 (1H, m), 2.57 (2H, d), 3.67 (3H, s), 4.32 (2H, s), 7.25 (1H, m), 7.30-7.40 (4H, m), 7.44 (1H, s).

Example 16

3-[(3-Hydroxypropy)thio]-5-methyl-7-(2-methylpropyl)-2-phenylmethylthieno[2,3-d]pyridazin-4(5H)-one



A solution of butyl lithium in hexanes (2.5M, 1.3ml) was added to a solution of diisopropylamine (0.45ml) in tetrahydrofuran (6ml) at 0°C under nitrogen. After 30 minutes, 5ml of the resulting solution was added to a solution of 5-methyl-7-(2-methylpropyl)-2-phenylmethylthieno[2,3-d]pyridazin-4(5H)-one (example 15, 0.50g) and S-[3-{[(1,1-dimethylethyl)dimethylsilyl]oxy}propyl] 4-methylbenzenesulfonothioate, (J. Med. Chem. 1995, 38, 2557., 0.85g) in tetrahydrofuran (10ml) at -78°C under nitrogen. The reaction mixture was warmed to room temperature, quenched with saturated aqueous ammonium chloride solution (25ml) and extracted with ethyl acetate (50ml). The organic extracts were washed twice with saturated aqueous ammonium chloride solution, twice with saturated sodium hydrogen carbonate solution, then with brine, dried, filtered and evaporated. The residue was dissolved in acetonitrile (20ml) and treated with 40% hydrofluoric acid (1ml). After 16 hours, saturated sodium hydrogen carbonate solution (50ml) was added and the mixture was extracted with ethyl acetate (50ml). The organic extracts were washed with brine, dried, filtered and evaporated. The residue was purified by column chromatography, eluting with ethyl acetate : isohexane (1:2 then 1:1) to give the title compound (0.51g) as a solid.

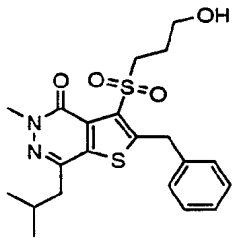
Melting point: 60-65°C

MS (+ve APCI) 403 ($(M+H)^+$)

^{1}H NMR (DMSO d6) δ 0.88 (6H, d), 1.57 (2H, quin), 2.08 (1H, m), 2.53 (2H, d), 3.00 (2H, t), 3.43 (2H, q), 3.70 (3H, s), 4.44 (2H, s), 4.48 (1H, t), 7.22-7.34 (5H, m).

Example 17

3-[(3-Hydroxypropyl)sulfonyl]-5-methyl-7-(2-methylpropyl)-2-phenylmethylthieno-[2,3-d]pyridazin-4(5H)-one



Prepared from 3-{[3-hydroxypropyl]thio}-5-methyl-7-(2-methylpropyl)-2-phenylmethylthieno[2,3-d]pyridazin-4(5H)-one (Example 16, 0.32g) and 3-chloroperoxybenzoic acid (86%, 0.32g) in dichloromethane (20ml) according to the procedure of example 13 to give the title compound (0.18g) as a foam.

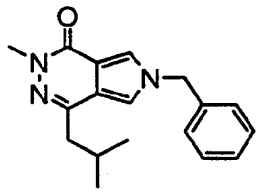
Melting point: 105-107°C

MS (+ve APCI) 435 ($(M+H)^+$)

^{1}H NMR (DMSO d6) δ 0.89 (6H, d), 1.74-1.83 (2H, m), 1.99-2.10 (1H, m), 2.57 (2H, d), 3.44 (2H, q), 3.71 (3H, s), 3.86-3,92 (2H, m), 4.63 (1H, t), 4.75 (2H, s), 7.28-7.38 (5H, m).

Example 18

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-phenylmethyl-1H-pyrrolo[3,4-d]pyridazin-1-one



a) **2,6-Dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one**

Methyl 4-(3-methyl-1-oxobutyl)-1H-pyrrole-3-carboxylate (Example 1 step b, 0.7g) and methylhydrazine (0.6 ml) in ethanol (20 ml) were heated under reflux for 16 hours.

The solution was evaporated, and the residue was partitioned between ethyl acetate and dilute hydrochloric acid. The organic phase was dried and evaporated to give 2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one as a red oil (0.65g).

MS (+ve APCI) 206 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 0.97 (6H, d), 2.08-2.32 (1H, m), 2.62 (2H, m), 3.78 (3H, s), 7.24 (1H, t), 7.57 (1H, t), 11.56 (1H, br).

b) **2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-phenylmethyl-1H-pyrrolo[3,4-d]pyridazin-1-one**

A solution of 2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one (0.65g) in dry dimethyl formamide (3 ml) was added dropwise to sodium hydride (0.15g of a 60% dispersion in oil) in dimethyl formamide (10 ml) with stirring. After 20 minutes benzyl bromide (0.45 ml) and a crystal of potassium iodide were added. The mixture was stirred for 11 days and then poured into dilute hydrochloric acid, which was extracted with ethyl acetate. The organic phase was washed with water, dried, and evaporated to give an oil, which was purified by chromatography on silica (ethyl acetate/isohexane 3:1) to afford, after crystallisation from cyclohexane, 2,6-dihydro-2-methyl-4-(2-methylpropyl)-6-phenylmethyl-1H-pyrrolo[3,4-d]pyridazin-1-one (0.3g).

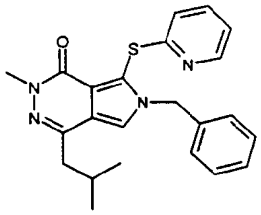
Melting point: 104°C

MS (+ve APCI) 296 ((M+H)+)

^{1}H NMR ($CDCl_3$) δ 0.95 (6H, s), 2.12 (1H, m), 2.56 (2H, d), 3.72 (3H, s), 5.27 (2H, s), 7.08 (1H, d(J=2.1Hz)), 7.16 (2H, m), 7.37 (3H, m), 7.49 (1H, d(J=2.1Hz)).

Example 19

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-phenylmethyl-7-(2-pyridinylthio)-1H-pyrrolo[3,4-d]pyridazin-1-one



Butyl lithium (2.5M in hexanes, 0.32ml) was added dropwise to a stirred solution of diisopropylamine (0.11ml) in dry tetrahydrofuran (2ml) at 0°C, under nitrogen. The reaction was stirred at 0°C for 30 minutes, then cooled to -78°C. To this was added a solution of 2,6-dihydro-2-methyl-4-(2-methylpropyl)-6-(1-phenylmethyl)-1H-pyrrolo[3,4-d]pyridazin-1-one (Example 18, 0.2g) in dry tetrahydrofuran (2ml), and stirring was continued for 30 minutes. A solution of 2,2'-dipyridyl disulfide (0.155g) in dry tetrahydrofuran (2ml) was added. The reaction was allowed to warm to room temperature overnight, and was then quenched by the addition of saturated ammonium chloride solution. The mixture was extracted into diethylether, washed with brine, dried and evaporated to give a yellow oil. Chromatography, eluting with dichloromethane : acetone (4:1), followed by reverse phase HPLC, with an acetonitrile : aqueous ammonium acetate gradient, gave the title compound (0.05g).

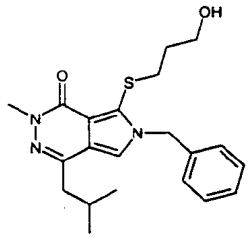
Melting point: 131-132°C

MS (+ve APCI) ($(M+H)^+$) 405

^{1}H NMR ($CDCl_3$) δ 0.97 (d, 6H), 2.06-2.19 (m, 1H), 2.55 (d, 2H), 3.70 (s, 3H), 5.44 (s, 2H), 6.88 (d, 1H), 6.93 (dd, 1H), 7.10-7.12 (m, 2H), 7.25-7.27 (m, 4H), 7.40 (t, 1H), 8.32 (d, 1H).

Example 20

2,6-Dihydro-7-[(3-hydroxypropyl)thio]-2-methyl-4-(2-methylpropyl)-6-phenylmethyl-1H-pyrrolo[3,4-d]pyridazin-1-one



Butyl lithium (2.5M in hexanes, 0.32ml) was added dropwise to a stirred solution of diisopropylamine (0.11ml) in dry tetrahydrofuran (2ml) at 0°C, under nitrogen. The reaction was stirred at 0°C for 30 minutes, then cooled to -78°C. To this solution was added a solution of 2,6-dihydro-2-methyl-4-(2-methylpropyl)-6-phenylmethyl-1H-pyrrolo[3,4-d]pyridazin-1-one (Example 18, 0.2g) in dry tetrahydrofuran (2ml), and stirring was continued for 30 minutes. A solution of S-[3-{[(1,1-dimethylethyl)dimethylsilyl]oxy}propyl] 4-methylbenzenesulfonothioate, (J. Med. Chem. 1995, 38, 2557., 0.25g) in dry tetrahydrofuran (2ml) was added. The reaction was allowed to warm to room temperature overnight, and was then quenched by the addition of saturated ammonium chloride solution. The mixture was extracted into diethylether, washed with brine, dried and evaporated. Chromatography, eluting with ethyl acetate : isohexane (3:7), gave a yellow oil (0.24g), MS (APCI) 500 $(M+H)^+$.

To a stirred solution of this oil (0.24g) in methanol (2ml) was added concentrated hydrochloric acid (0.25ml). After 2 hours, the reaction was made alkaline by the addition of saturated sodium hydrogen carbonate solution. The mixture was extracted into ethyl acetate, washed with brine, dried and evaporated. Chromatography, eluting with ethyl acetate, followed by trituration with isohexane : diethylether gave the title compound (0.105g).

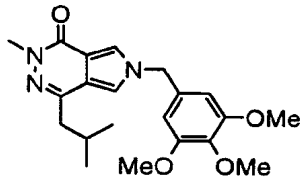
Melting point: 91-92°C

MS (+ve APCI) ($(M+H)^+$) 386

^{1}H NMR (DMSO d-6) δ 0.92 (d, 6H), 1.46 (quint, 2H), 2.04-2.14 (m, 1H), 2.53 (d, 2H), 2.88 (t, 2H), 3.30-3.37 (m, 2H), 3.55 (s, 3H), 4.44 (t, 1H), 5.52 (s, 2H), 7.11 (s, 1H), 7.14 (d, 1H), 7.25-7.37 (m, 3H), 7.88 (s, 1H).

Example 21

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(3,4,5-trimethoxyphenyl)methyl-1H-pyrrolo[3,4-d]pyridazin-1-one



A mixture of 2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one (Example 18 step a, 0.031g), 3,4,5-trimethoxybenzyl chloride (0.038g), and cesium carbonate (0.090g) in dry dimethyl formamide (0.8 ml) was stirred for 16 hours, and then diluted with dilute hydrochloric acid. The mixture was extracted with ethyl acetate, which was washed with brine, dried, and evaporated to a solid. The solid was purified by chromatography on silica (dichloromethane/ethanol 9:1) to give 2,6-dihydro-2-methyl-4-(2-methylpropyl)-6-[3,4,5-trimethoxyphenyl]methyl-1H-pyrrolo[3,4-d]pyridazin-1-one (0.033g).

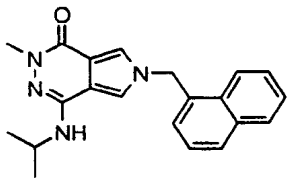
Melting point: 154.5-155°

MS (+ve APCI) 386 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 0.96 (6H, d), 2.14 (1H, m), 2.56 (2H, d), 3.73 (3H, s), 3.81 (6H, s), 3.84 (3H, s), 5.19 (2H, s), 6.37 (2H, s), 7.01 (1H, d(J=2.1Hz)), 7.50 (1H, d(J=1.8Hz)).

Example 22

2,6-Dihydro-2-methyl-6-(1-naphthalenylmethyl)-4-(1-methylethyl)amino-1H-pyrrolo[3,4-d]pyridazin-1-one



a) **Diethyl 1-(1-naphthalenylmethyl)pyrrole-3,4-dicarboxylate**

Potassium carbonate (5g) followed by 1-(chloromethyl)naphthalene (4.60g) were added to a solution of diethyl 3,4-pyrroledicarboxylate (5.00g) in acetone (50ml). The mixture was stirred at room temperature for 4 days, dilute hydrochloric acid (100ml) was added and the mixture was extracted with ether (2 × 100ml). The organic extracts were dried, filtered and evaporated to give the sub-title compound as a solid (7.62g).

^{1}H NMR ($CDCl_3$) δ 1.31 (6H, t), 4.27 (4H, q), 5.49 (2H, s), 7.21-7.28 (3H, m), 7.46 (1H, t), 7.50-7.57 (2H, m), 7.80-7.93 (3H, m).

b) **2,3-Dihydro-2-methyl-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyridazine-1,4(6H)-dione**

Methyl hydrazine (0.55ml) was added to a solution of diethyl 1-(1-naphthalenylmethyl)pyrrole-3,4-dicarboxylate (1.00g) in ethanol (10ml). The mixture was heated at 200°C in a sealed tube for 3 days. The mixture was evaporated and the residue was purified by column chromatography, eluting with ethyl acetate : methanol (19:1) . The resulting solid was suspended in ethyl acetate (25ml), heated to reflux, and allowed to cool to ambient temperature. The title compound (0.105g) was collected by filtration.

MS (+ve APCI) 306 ($(M+H)^+$)

^{1}H NMR (DMSO d6) δ 3.33 (3H, s), 5.88 (2H, s), 7.32 (1H, d), 7.50-7.64 (5H, m), 7.94 (1H, d), 7.99 (1H, d), 8.19 (1H, d), 10.94 (1H, s, br).

c) **4-Chloro-2,6-dihydro-2-methyl-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyridazine-1-one**

A suspension of 2,3-dihydro-2-methyl-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyridazine-1,4(6H)-dione (0.10g) in phosphorus oxychloride (1ml) was heated at reflux for 30 minutes and then allowed to cool. The solvent was evaporated, water (25ml) was added and the mixture was extracted with ethyl acetate (2 × 25ml). The organic extracts were dried, filtered and evaporated to give the sub-title compound (0.095g).

MS (+ve APCI) 324/326 ($(M+H)^+$)

d) **2,6-Dihydro-2-methyl-6-(1-naphthalenylmethyl)-4-(2-propyl)amino-1H-pyrrolo[3,4-d]pyridazin-1-one**

Isopropylamine (1ml) was added to a solution of 4-chloro-2,6-dihydro-2-methyl-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyridazine-1-one (0.095g) in ethanol (4ml) and the mixture was heated in a sealed tube at 200°C for 3 days then at 250°C for 24 hours. The mixture was evaporated and the residue was purified by column chromatography, eluting with ethyl acetate followed by recrystallisation from ethyl acetate/isohexane to give the title compound (0.013g).

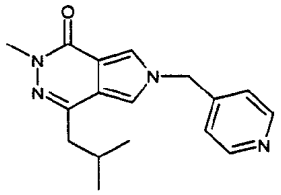
Melting point: 221-222°C

MS (+ve APCI) 347 ($(M+H)^+$)

^{1}H NMR (DMSO d6) δ 1.12 (6H, d), 3.39 (3H, s), 3.80-3.92 (1H, m), 5.86 (2H, s), 5.98 (1H, d), 7.34 (1H, d), 7.40 (1H, d), 7.44-7.60 (3H, m), 7.72 (1H, d), 7.95-8.01 (2H, m), 8.07-8.10 (1H, m).

Example 23

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(4-pyridinyl)methyl-1H-pyrrolo[3,4-d]pyridazin-1-one



a) **2,6-Dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one.**

Methyl 4-(3-methyl-1-oxobutyl)-1H-pyrrole-3-carboxylate (Example 1, step b, 7.8g) and methylhydrazine (6ml) were heated at reflux for 18 hours. The solvent was evaporated and the residue was chromatographed, eluting with dichloromethane-ethanol (19:1), to give the sub-title compound as a sand coloured solid (5.2g).

MS (+ve APCI) ($(M+H)^+$) 206

^{1}H NMR (DMSO d-6) δ 0.91 (d, 6H), 2.05-2.18 (m, 1H), 2.54 (d, 2H), 3.54 (s, 3H), 7.46 (t, 1H), 7.57 (t, 1H), 12.51 (br s, 1H).

b) **2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(4-pyridinyl)methyl-1H-pyrrolo[3,4-d]pyridazin-1-one**

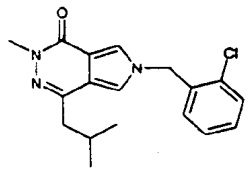
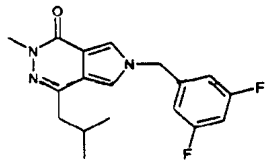
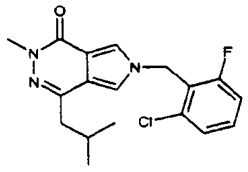
A mixture of 2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one (0.04g, Example 23, step a), cesium carbonate (0.2g), 4-chloromethylpyridine hydrochloride (0.035g) in dimethylformamide (4.5ml) was shaken periodically over 18 hours. The reaction was evaporated at reduced pressure, and the residue was purified by normal phase HPLC, eluting with a dichloromethane : ethanol gradient, to give the title compound (0.024g).

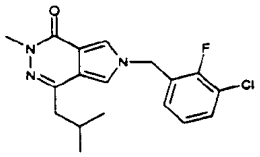
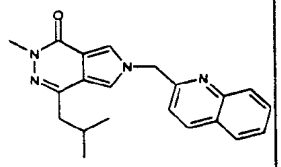
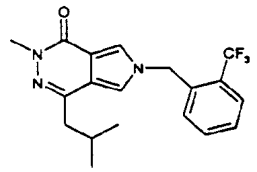
Melting point: 91-93°C

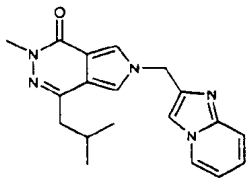
MS (+ve APCI) ($(M+H)^+$) 297

^{1}H NMR ($CDCl_3$) δ 0.96 (d, 6H), 2.07-2.20 (m, 1H), 2.56 (d, 2H), 3.73 (s, 3H), 5.30 (s, 2H), 6.98-7.01 (m, 3H), 7.51 (d, 1H), 8.61 (d, 2H).

The following examples were prepared and purified following the method of Example 23 step b from 2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one, cesium carbonate and the appropriate benzyl halide.

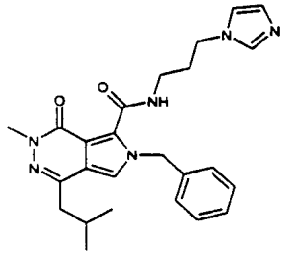
Example	Name	Melting point °C	MS (+ve APCI) ($(M+H)^+$)	^{1}H NMR ($CDCl_3$) δ
24 	6-(2-Chlorophenyl)-methyl-2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]-pyridazin-1-one	102-104	330/332	0.97 (d, 6H), 2.06-2.19 (m, 1H), 2.56 (d, 2H), 3.72 (s, 3H), 5.38 (s, 2H), 6.96 (1H, dd), 7.05 (1H, d), 7.22-7.34 (2H, m) 7.43 (1H, dd), 7.49 (1H, d)
25 	6-(3,5-Difluorophenyl)-methyl-2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]-pyridazin-1-one	172-174	332	0.97 (d, 6H), 2.06-2.20 (m, 1H), 2.56 (d, 2H), 3.73 (s, 3H), 5.25 (s, 2H), 6.60-6.68 (m, 2H), 6.79 (tt, 1H), 7.00 (d, 1H), 7.48 (d, 1H)
26 	6-(2-Chloro-6-fluorophenyl)methyl-2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]-pyridazin-1-one	124-126	348/350	0.96 (d, 6H), 2.07-2.20 (m, 1H), 2.55 (d, 2H), 3.70 (s, 3H), 5.44 (s, 2H), 7.06-7.12 (m, 2H), 7.28-7.37 (m, 2H), 7.55 (d, 1H).

Example	Name	Melting point °C	MS (+ve APCI) ($(M+H)^+$)	^{1}H NMR ($CDCl_3$) δ
27 	6-(3-Chloro-2-fluorophenyl)methyl-2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]-pyridazin-1-one	124-127	348/350	0.96 (d, 6H), 2.07-2.20 (m, 1H), 2.55 (d, 2H), 3.72 (s, 3H), 5.33 (s, 2H), 6.95 (t, 1H), 7.04-7.11 (m, 2H), 7.41 (t, 1H), 7.50 (d, 1H)
28 	2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(2-quinolinylmethyl)-1H-pyrrolo[3,4-d]-pyridazin-1-one	141-143	347	0.95 (d, 6H), 2.07-2.20 (m, 1H), 2.55 (d, 2H), 3.73 (s, 3H), 5.57 (s, 2H), 7.05 (d, 1H), 7.14 (d, 1H), 7.55-7.63 (m, 2H), 7.74-7.83 (m, 2H), 8.09 (d, 1H), 8.13 (d, 1H)
29 	2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(2-trifluoromethyl-phenyl)methyl-1H-pyrrolo[3,4-d]-pyridazin-1-one	127-129	364	0.96 (d, 6H), 2.06-2.20 (m, 1H), 2.56 (d, 2H), 3.73 (s, 3H), 5.49 (s, 2H), 6.85(d, 1H), 7.02 (d, 1H), 7.42-7.52 (m, 3H), 7.74 (d, 1H)

Example	Name	Melting point °C	MS (+ve APCI) ($(M+H)^+$)	^{1}H NMR ($CDCl_3$) δ
30 	2,6-Dihydro-6-(2-imidazo[1,2-a]-pyridinyl)methyl-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]-pyridazin-1-one	165-166	336	0.96 (d, 6H), 2.07-2.21 (m, 1H), 2.55 (d, 2H), 3.71 (s, 3H), 5.43 (s, 2H), 6.81 (t, 1H), 7.19 (d, 1H), 7.22 (dd, 1H), 7.43 (s, 1H), 7.56-7.60 (m, 2H), 8.05 (dd, 1H)

Example 31

2,6-Dihydro-N-[3-(1-1H-imidazolyl)propyl]-2-methyl-4-(2-methylpropyl)-1-oxo-6-phenylmethyl-1H-pyrrolo[3,4-d]pyridazin-1-one-5-carboxamide



a) 2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-phenylmethyl-1H-pyrrolo[3,4-d]pyridazin-1-one-5-carboxylic acid.

Butyl lithium (2.5M in hexanes, 2.35ml) was added dropwise to a stirred solution of diisopropylamine (0.85ml) in dry tetrahydrofuran (10ml) at 0°C, under nitrogen. The reaction was stirred at 0°C for 30 minutes, then cooled to -78°C. To this was added a solution of 2,6-dihydro-2-methyl-4-(2-methylpropyl)-6-(1-phenylmethyl)-1H-pyrrolo[3,4-d]pyridazin-1-one (1.5g, prepared as in Example 14 step b) in dry tetrahydrofuran (10ml), and stirring was continued for 30 minutes. This anion was then added to an excess of solid carbon dioxide. The reaction was allowed to warm to room temperature overnight, and was then quenched by the addition of water. The mixture was extracted into ethyl acetate, washed with brine, dried and evaporated to give a yellow oil, which was chromatographed,

eluting with ethyl acetate : isohexane(3:7), to give the sub-title compound as a yellow solid (0.91g).

Melting point: 129-130°C

MS (+ve APCI) ($(M+H)^+$) 340

^{1}H NMR ($CDCl_3$) δ 0.96 (d, 6H), 2.04-2.18 (m, 1H), 2.61 (d, 2H), 3.82 (s, 3H), 5.99 (s, 2H), 7.22-7.38 (m, 6H), 16.43 (s, 1H).

b) 2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-phenylmethyl-1H-pyrrolo[3,4-d]pyridazin-1-one-5-carboxylic acid, 3-(1-imidazolyl)propyl amide

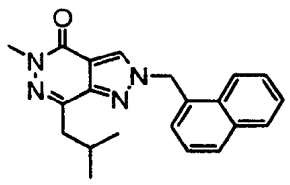
A mixture of 2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-phenylmethyl-1H-pyrrolo[3,4-d]pyridazin-1-one-5-carboxylic acid (0.04g), hydroxybenzotriazole (0.5ml, 0.49M in dimethylformamide), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.5ml, 0.47M in dimethylformamide) and N-(3-aminopropyl)imidazole (0.03g) in dimethylformamide (3ml) were shaken periodically over 48 hours. The solvent was evaporated, and the residue was chromatographed, eluting with dichloromethane : ethanol (19:1) to give the title compound (0.011g).

MS (+ve APCI) ($(M+H)^+$) 447

^{1}H NMR ($CDCl_3$) δ 0.98 (d, 6H), 2.12-2.20 (m, 3H), 2.62 (d, 2H), 3.40 (q, 2H), 3.82 (s, 3H), 4.15 (q, 2H), 6.05 (s, 2H), 7.10 (d, 2H), 7.20 (s, 1H), 7.30-7.40 (m, 5H), 8.61 (s, 1H), 11.81 (t, 1H).

Example 32

2,5-Dihydro-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4H-pyrazolo[3,4-d]pyridazin-4-one



a) **Ethyl 4-hydroxy-6-methyl-2-heptynoate**

n-Butyl lithium (2.5M in hexanes, 22.5 ml) was added dropwise over 40 minutes with stirring to fresh ethyl propiolate (6.0 ml) in dry tetrahydrofuran (75 ml) under nitrogen, with the temperature being maintained below -68° by external cooling. After 30 minutes, isovaleraldehyde (6.5 ml) in dry tetrahydrofuran (15 ml) was added over 15 minutes with the temperature maintained below -69°. After one hour, trimethylsilyl chloride (10 ml) was added and the reaction was allowed to warm to room temperature. Water was added and the mixture was extracted with ethyl acetate, which was washed with brine, dried, and evaporated to give ethyl 4-hydroxy-6-methyl-2-heptynoate as an oil (9.5g).

GC/MS (after BSTMA) EI: 241(M-15)

b) **Ethyl 6-methyl-4-oxo-2-heptynoate**

Jones' reagent (from chromium trioxide, 4g) was added dropwise with stirring to ethyl 4-hydroxy-6-methyl-2-heptynoate (9.5g) in acetone (30 ml) in an ice bath, with the temperature being maintained at about 10°. After 0.5 hour the reaction was diluted with water (300 ml) and extracted with diethyl ether thrice. The organic phase was washed with brine, dried, and evaporated to give ethyl 6-methyl-4-oxo-2-heptynoate as an oil (7.0g).

GC/MS EI: 167 (M-15)

^{1}H NMR ($CDCl_3$) δ 0.97 (6H, d), 1.30 (3H, t), 2.20 (1H, m), 2.51 (2H, d), 4.30 (2H, q).

c) **Ethyl 5-(3-methyl-1-oxobutyl)-1H-pyrazole-4-carboxylate, and ethyl 4-(3-methyl-1-oxobutyl)-1H-pyrazole-5-carboxylate**

(Trimethylsilyl)diazomethane (2.0M in hexanes, 25 ml) was added slowly with stirring under nitrogen to ethyl 6-methyl-4-oxo-2-heptynoate (7.0g) in dry tetrahydrofuran (20 ml) in a cold water bath. After 16 hours the reaction was evaporated to an oil, which was subjected to chromatography on silica (ethyl acetate/isohexane 1:2) to give the first eluted product, ethyl 5-(3-methyl-1-oxobutyl)-1H-pyrazole-4-carboxylate (2.33g).

Melting point: 105-107°C

MS (+ve APCI) 225 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 0.99 (6H, d), 1.38 (3H, t), 2.25 (1H, m), 3.07 (2H, d), 4.35 (2H,q), 8.12 (1H, s), 11.5 (1H,br).

The second eluted product was ethyl 4-(3-methyl-1-oxobutyl)-1H-pyrazole-5-carboxylate (1.22g).

Melting point: 61-62°C

MS (+ve APCI) 226 ((M+H)+)

^{1}H NMR ($CDCl_3$) δ 0.98 (6H, d), 1.42 (3H, t), 2.23 (1H, m), 2.79 (2H, d), 4.46 (2H,q), 8.09 (1H, s), 12.55 (1H, br).

d) **Ethyl 3-(3-methyl-1-oxobutyl)-1-(1-naphthalenylmethyl)-1H-pyrazole-4-carboxylate**

Ethyl 5-(3-methyl-1-oxobutyl)-1H-pyrazole-4-carboxylate (0.75g), 1-naphthalenemethyl chloride (0.6g), and cesium carbonate (1.25g) in dry dimethyl formamide (15 ml) were stirred under nitrogen for 24 hours, and then dilute hydrochloric

acid was added. The mixture was extracted with ethyl acetate, which was washed with brine, dried, and evaporated to give the sub-title compound as a gum.

MS AP+ve 365 (M+1)

^{1}H NMR ($CDCl_3$) δ 0.98 (6H, d), 1.26 (3H, t), 2.21-2.37 (1H, m), 2.92 (2H, d), 4.21 (2H, q), 5.77 (2H, s), 7.39-7.57 (2H, m), 7.50 (1H, d), 7.61 (1H, s), 7.80-7.95 (2H, m), 7.95 (1H, d).

e) **2,5-Dihydro-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4H-pyrazolo[3,4-d]pyridazin-4-one**

Ethyl 3-(3-methyl-1-oxobutyl)-1-(1-naphthalenylmethyl)-1H-pyrazole-4-carboxylate (1.8g) and methylhydrazine (0.6 ml) in ethanol (20 ml) were heated under reflux for 16 hours. The solution was cooled and evaporated to a solid, which was purified by chromatography on silica (ethyl acetate : isohexane 2:3) followed by crystallisation from ethyl acetate/cyclohexane to give 2,5-dihydro-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4H-pyrazolo[3,4-d]pyridazin-4-one (0.43g).

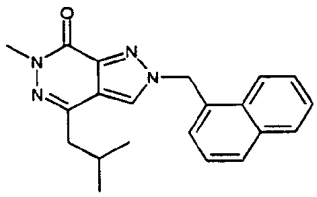
Melting point 166-167°

MS (+ve APCI) 347 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 1.02 (6H, d), 2.38 (1H, m), 2.82 (2H, d), 3.71 (3H, s), 5.97 (2H, s), 7.35-7.50 (4H, m), 7.86 (1H, s), 7.86 (1H, d), 7.91 (1H, d), 7.93 (1H, d).

Example 33

2,6-Dihydro-6-methyl-4-(2-methylpropyl)-2-(1-naphthalenylmethyl)-7H-pyrazolo[3,4-d]pyridazin-7-one



a) **Ethyl 4-(3-methyl-1-oxobutyl)-1-(1-naphthalenylmethyl)-1H-pyrazole-3-carboxylate**

Ethyl 4-(3-methyl-1-oxobutyl)-1H-pyrazole-5-carboxylate (Example 32, step c; 0.62g), 1-naphthalenylmethyl chloride (0.53g), and cesium carbonate (1.1g) were stirred in dry dimethylformamide (8 ml) for 48 hours, and then dilute hydrochloric acid was added. The mixture was extracted with ethyl acetate, which was washed with brine, dried, and evaporated to give ethyl 4-(3-methyl-1-oxobutyl)-1-(1-naphthalenylmethyl)-1H-pyrazole-3-carboxylate as a gum. (0.15g)

MS (+ve APCI) 365 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 0.87 (6H, d), 1.43 (3H, t), 2.12 (1H, m), 2.66 (2H, d), 4.47 (2H, q), 5.80 (2H, s), 7.50 (1H, s), 7.4-7.6 (4H, m), 7.8-7.9 (3H, m)

b) **2,6-Dihydro-6-methyl-4-(2-methylpropyl)-2-(1-naphthalenylmethyl)-7H-pyrazolo[3,4-d]pyridazin-7-one**

A mixture of ethyl 4-(3-methyl-1-oxobutyl)-1-(1-naphthalenylmethyl)-1H-pyrazole-3-carboxylate (0.15g) and methylhydrazine (0.1ml) in ethanol (2ml) was heated at reflux for 18 hours. The reaction was diluted with water and then extracted into ethyl acetate. The organic phase was washed with brine, dried, filtered and evaporated. The residue was chromatographed, eluting with dichloromethane : ethanol (19:1), to give the title compound (0.08g).

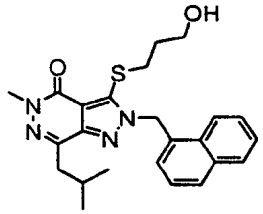
Melting point 163-164°C

MS (+ve APCI) ($(M+H)^+$) 347

^1H NMR ($CDCl_3$) δ 0.85 (d, 6H), 1.89-2.03 (m, 1H), 2.44 (d, 2H), 3.80 (s, 3H), 6.03 (s, 2H), 7.46-7.55 (m, 5H), 7.90-7.96 (m, 3H).

Example 34

2,5-Dihydro-3-[(3-hydoxypropyl)thio]-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4H-pyrazolo[3,4-d]pyridazin-4-one



Lithium diisopropylamide (0.4M in tetrahydrofuran, 2.0 ml) was added slowly to a solution of 2,5-dihydro-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4H-pyrazolo[3,4-d]pyridazin-4-one (0.17g) and S-[3-{[(1,1-dimethylethyl)-dimethylsilyl]oxy}propyl] 4-methylbenzenesulfonothioate, (J. Med. Chem. 1995, 38, 2557., 0.34g) in dry tetrahydrofuran (7 ml) stirred at -78° under nitrogen. After 3 hours saturated sodium hydrogen carbonate solution was added, and the mixture was allowed to warm to ambient temperature and then extracted with ethyl acetate. The organic phase was washed with brine, dried, and evaporated to an oil (0.4g). The oil was dissolved in acetonitrile (7 ml) and treated with hydrofluoric acid (40%, 0.4 ml). After 16 hours an excess of sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate, which was then washed with brine, dried, and evaporated. The residue was purified by chromatography on silica (ethyl acetate : isohexane 2:1) to give a solid which was crystallised from cyclohexane/ethyl acetate to afford 2,5-dihydro-3-[(3-hydoxypropyl)thio]-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4H-pyrazolo[3,4-d]pyridazin-4-one (0.135g).

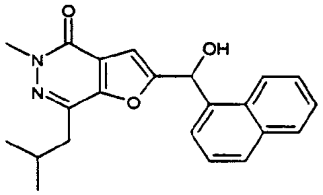
Melting point 141-142°C

MS (+ve APCI) 437 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 0.97 (6H, d), 1.76 (2H, quint), 2.30 (1H, m), 2.76 (2H, d), 3.27 (2H, t), 3.43 (1H, t), 3.76 (3H, s), 3.80 (2H, q), 6.18 (2H, s), 6.88 (1H, d), 7.3-7.6 (3H, m), 7.81 (1H, d), 7.90 (1H, d), 8.27 (1H, d).

Example 35

2-[1-Hydroxy-1-(1-naphthalenyl)methyl]-5-methyl-7-(2-methylpropyl)furo[2,3-d]pyridazin-4(5H)one



a) **2-(1-Hydroxy-3-methylbutyl)furan-3-carboxylic acid**

3-Furoic acid (2.85g) was dissolved in tetrahydrofuran (50ml) and cooled to -78°C. A solution of lithium diisopropylamide (56mmol) in tetrahydrofuran (100ml) was added dropwise and the mixture was stirred for 15 minutes. A solution of 3-methylbutanal (3.0ml) in tetrahydrofuran (15ml) was added dropwise. The reaction mixture was stirred at -78°C for 1h and then allowed to warm to ambient temperature. The mixture was poured into water, the aqueous phase was acidified with 2M hydrochloric acid and the mixture was extracted twice with ethyl acetate. The organic phases were washed with brine, dried, filtered and evaporated. Chromatography, eluting with dichloromethane : ethyl acetate : acetic acid (160:40:1), gave the sub-title compound (2.75g).

MS (-ve APCI) 197 ($(M-H)^-$)

^{1}H NMR ($CDCl_3$) δ 0.96 (6H, m), 1.62-1.89 (3H, m), 5.12 (1H, dd), 6.73 (1H, d), 7.32 (1H, d).

b) **Trimethylsilylmethyl 2-(1-hydroxy-3-methylbutyl)furan-3-carboxylate**

2-(1-Hydroxy-3-methylbutyl)furan-3-carboxylic acid (800mg) was dissolved in dichloromethane (30ml) and a solution of trimethysilyldiazomethane (2M in hexane, 2.1ml) was added. The mixture was stirred for 20h, then diluted with dichloromethane and

washed twice with hydrochloric acid. The organic phase was washed with brine, then dried, filtered and evaporated. Chromatography, eluting with diethylether : isohexane (1:1), gave the sub-title compound (435mg).

MS (+ve APCI) 267 $((M-Me)^+)$

^1H NMR ($CDCl_3$) δ 0.12 (9H, s), 0.95 (6H, dd), 1.60-1.88 (3H, m), 3.96 (2H, s), 4.37 (1H, d), 5.01 (1H, m), 6.64 (1H, d), 7.26 (1H, d),.

c) **Trimethylsilylmethyl 2-(3-methyl-1-oxobutyl)furan-3-carboxylate**

Dimethylsulfoxide (125µl) was dissolved in dichloromethane (10ml) and cooled to -78°C. Oxalyl chloride (80µl) was added dropwise and the mixture was stirred for 15 minutes. Trimethylsilylmethyl 2-(1-hydroxy-3-methylbutyl)furan-3-carboxylate (200mg) in dichloromethane (10ml) was added and the mixture was stirred for 20 minutes. Triethylamine (0.49ml) was added. The mixture was stirred for 20 minutes, and then allowed to warm to ambient temperature. The mixture was poured onto water and then extracted thrice with ethyl acetate. The organic phases were combined, washed with brine, dried, filtered and evaporated to give the sub-title compound (170mg).

MS (+ve APCI) 283 $((M+H)^+)$

d) **5-Methyl-7-(2-methylpropyl)furo[2,3-dpyridazin-4(5H)-one**

Trimethylsilylmethyl 2-(3-methyl-1-oxobutyl)furan-3-carboxylate (170mg) and methyl hydrazine (40µl) were combined in xylene (10ml) and the mixture was heated under reflux for 5 hours. The mixture was allowed to cool to ambient temperature, poured onto water and then extracted twice with ethyl acetate. The combined organic phases were washed with brine, dried, filtered and evaporated. Chromatography, eluting with isohexane : ethyl acetate (3:2), gave the sub-title compound (49mg).

MS (+ve APCI) 207 $((M+H)^+)$

^1H NMR ($CDCl_3$) δ 0.98 (6H, d), 2.12-2.26 (1H, d), 2.73 (2H, d), 3.84 (3H, s), 7.05 (1H, d), 7.65 (1H, d).

e) **2-[1-Hydroxy-1-(1-naphthalenyl)methyl]-5-methyl-7-(2-methylpropyl)furo[2,3-d]pyridazin-4(5H)-one**

5-Methyl-7-(2-methylpropyl)furo[2,3-dpyridazin-4(5H)-one (105mg) was dissolved in tetrahydrofuran (5ml) and cooled to -78°C. Lithium diisopropylamide in tetrahydrofuran (1M, 0.56ml) was added to the solution and the mixture was stirred for 30 minutes. 1-Naphthaldehyde (80µl) was added and the reaction was stirred for 30 minutes, and then allowed to warm to ambient temperature. The mixture was poured onto water and extracted thrice with ethyl acetate. The combined organic phases were washed with brine, dried, filtered and evaporated. Chromatography, eluting with isohexane : ethyl acetate (1:1), gave the title compound (50mg).

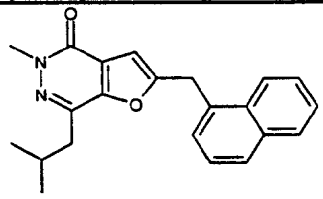
Melting point 110-112°C

MS (+ve APCI) 363 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 0.91 (6H, dd), 2.04-2.18 (1H, m), 2.67 (2H, d), 2.81 (1H, d), 3.79 (3H, s), 6.66 (1H, d), 6.73,(1H, s), 7.48-7.53 (3H, m), 7.65 (1H, d), 7.87-7.91 (2H, m), 8.04-8.06 (1H, m).

Example 36

5-Methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)furo[2,3-d]pyridazin-4(5H)one



2-[1-Hydroxy-1-(1-naphthalenyl)methyl]-5-methyl-7-(2-methylpropyl)furo[2,3-d]pyridazin-4(5H)one (68mg) was dissolved in dichloromethane (3ml). Trifluoroacetic acid (1ml) and triethylsilane (1ml) were added and the mixture was stirred for 24 hours. The mixture was poured onto 2M sodium hydroxide solution and was then extracted twice with ethyl acetate. The combined organic phases were washed with brine, dried, filtered and evaporated. Chromatography, eluting with isohexane : ethyl acetate (1:1), gave the title compound (52mg).

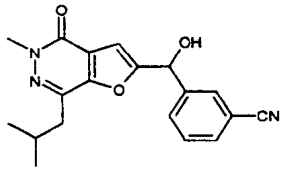
Melting point 73-75°C

MS (+ve APCI) 347 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 0.94 (6H, d), 2.08-2.22 (1H, m), 2.69 (2H, d), 3.79 (3H, s), 4.56 (2H, s), 6.50 (1H, s), 7.37-7.53 (4H, m), 7.81-7.99 (3H, m).

Example 37

2-[1-Hydroxy-1-(3-cyanophenyl)methyl]-5-methyl-7-(2-methylpropyl)furo[2,3-d]pyridazin-4(5H)one



Prepared from 5-methyl-7-(2-methylpropyl)furo[2,3-dpyridazin-4(5H)-one (example 35 step d) and 3-cyanobenzaldehyde following the method of Example 35 step e.

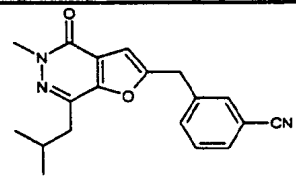
Melting point: 106-108°C

MS (+ve APCI) 338 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 0.93 (6H, d), 2.04-2.18 (1H, m), 2.67 (2H, d), 3.30 (1H, d), 3.81 (3H, s), 6.00 (1H, d), 6.81 (1H, s), 7.52 (1H, t), 7.67 (2H, m), 7.81 (1H, s).

Example 38

2-(3-Cyanophenyl)methyl-5-methyl-7-(2-methylpropyl)furo[2,3-d]pyridazin-4(5H)one



Prepared from 2-[1-hydroxy-1-(3-cyanophenyl)methyl]-5-methyl-7-(2-methylpropyl)furo[2,3-d]pyridazin-4(5H)one following the method of Example 36.

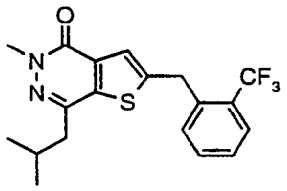
Melting point: 76-78°C

MS (+ve APCI) 322 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 0.95 (6H, d), 2.13 (1H, m), 3.68 (2H, d), 3.82 (3H, s), 4.17 (2H, s), 6.68 (1H, s), 7.44-7.52 (2H, m), 7.58-7.60 (2H, m).

Example 39

2-(2-Trifluoromethylphenyl)methyl-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one



A solution of lithium diisopropylamide (11.3mmol) in tetrahydrofuran/hexane (2:1, 16ml) was added dropwise to a solution of 5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one (Example 6 step b, 1.00g) in tetrahydrofuran (20ml) at -78°C under nitrogen. After 5 minutes, 2-trifluoromethylbenzaldehyde (1.57g) was added. The mixture was stirred at -78°C for 3 hours, then saturated sodium hydrogen carbonate solution (50ml) was added, and the mixture was warmed to room temperature and extracted with ethyl acetate (50ml). The organic extracts were washed twice with saturated sodium hydrogen carbonate solution, then with brine, then dried, filtered and evaporated. The residue was dissolved in trifluoroacetic acid (5ml) and triethylsilane (2ml) was added. After 24 hours, additional trifluoroacetic acid (5ml) and triethylsilane (2ml) were added. After a further 3 days, the mixture was diluted with water (50ml) and extracted with ethyl acetate (50ml). The organic extracts were washed twice with 1M sodium hydroxide solution, then with brine, and then dried, filtered and evaporated. The residue was purified by column chromatography, eluting with an ethyl acetate/isohexane gradient, followed by preparative normal-phase HPLC with gradient dichloromethane/ethanol elution and then with gradient ethyl acetate/isohexane elution to give the title compound (0.055g).

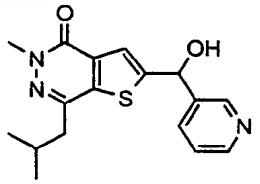
Melting point 112-114°C

MS (+ve APCI) 381 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 0.97 (6H, d), 2.12- 2.24 (1H, m), 2.59 (2H, d), 3.81 (3H, s), 4.41 (2H, s), 7.35-7.43 (3H, m), 7.53 (1H, t), 7.70 (1H, d).

Example 40

2-[(1-Hydroxy-1-pyridin-3-yl)methyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one hydrochloride



Reaction of 5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one (Example 6 step b 1.00g) and 3-pyridinecarboxaldehyde (0.96g) according to the procedure of example 14 gave the crude title compound as the free base. This material was purified by column chromatography, eluting with an ethyl acetate/ethanol gradient, then dissolved in ether (50ml) and treated with 4M hydrogen chloride in 1,4-dioxane (0.5ml). The precipitated solid was collected and dried in vacuo to give the title compound (0.06g).

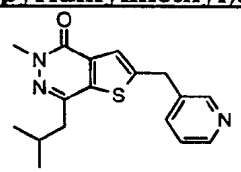
Melting point: 154-156°C

MS (+ve APCI) 330 ($(M+H)^+$)

^{1}H NMR (DMSO d6) δ 0.96 (6H, d), 1.39 (1H, s), 2.10-2.24 (1H, m), 2.59 (2H, d), 3.80 (3H, s), 6.16 (1H, s), 7.32 (1H, dd), 7.43 (1H, s), 7.81 (1H, dt), 8.55 (1H, dd), 8.68 (1H, d).

Example 41

5-Methyl-7-(2-methylpropyl)-2-(3-pyridinylmethyl)thieno[2,3-d]pyridazin-4(5H)-one



Prepared from 2-[(1-hydroxy-1-pyridin-3-yl)methyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one hydrochloride (example 40, 0.54g) according to the procedure for Example 43b. The crude product was purified by column

chromatography, eluting with ethyl acetate : methanol : aqueous ammonia solution (99:0:1, 94:5:1 then 89:10:1) followed by trituration with ether to give the title compound (0.30g).

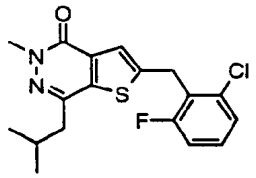
Melting point: 118-119°C

MS (+ve APCI) 314 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 0.96 (6H, d), 2.13-2.22 (1H, m), 2.59 (2H, d), 3.81 (3H, s), 4.25 (2H, s), 7.28 (1H, dd), 7.43 (1H, s), 7.57 (1H, d), 8.54-8.57 (2H, m).

Example 42

2-(2-Chloro-6-fluorophenyl)methyl-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one



Prepared from 5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one (example 6 step b 1.00g) and 2-chloro-6-fluorobenzaldehyde (0.96g) according to the procedure of Example 14. The crude product was purified by preparative normal-phase HPLC with gradient dichloromethane/ethanol elution followed by recrystallisation from isohexane to give the title compound (0.07g).

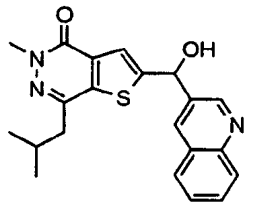
Melting point 85-86°C

MS (+ve APCI) 365/367 ($(M+H)^+$)

^{1}H NMR ($CDCl_3$) δ 0.97 (6H, d), 2.15-2.24 (1H, m), 2.59 (2H, d), 3.80 (3H, s), 4.39-4.40 (2H, s), 7.01-7.08 (1H, m), 7.19-7.26 (2H, m), 7.42 (1H, s).

Example 43

2-[(1-Hydroxy-1-quinolin-3-yl)methyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one

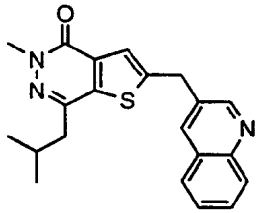


Prepared from 5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one (example 6 step b, 1.00g) and 3-quinolinecarboxaldehyde (1.06g) according to the procedure of example 14. The crude product was purified column chromatography, eluting with ethyl acetate : triethylamine (99:1) then ethyl acetate/methanol/triethylamine (89:10:1) to give the title compound (0.50g) as an oil.

MS (+ve APCI) 380 ($(M+H)^+$).

Example 44

5-Methyl-7-(2-methylpropyl)-2-(3-quinolinylmethyl)thieno[2,3-d]pyridazin-4(5H)-one hydrochloride



Thionyl chloride (0.10ml) was added to a solution of 2-[(1-hydroxy-1-quinolin-3-yl)methyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one in dichloromethane (8ml) at room temperature. After 3 hours, the solution was evaporated. The residue was dissolved in ethyl acetate (15ml). Triethylamine (0.50ml) was added and the solution was hydrogenated over palladium on carbon (5%, 0.035g) for 20 hours. The mixture was filtered, and the catalyst was washed with ethyl acetate (50ml). The filtrate was washed with water, then twice with saturated sodium hydrogen carbonate solution, and then with brine. The organic phase was dried, filtered and evaporated. The residue was

purified by column chromatography, eluting with ethyl acetate : isohexane : triethylamine (50:50:1, 66:33:1 then 100:0:1). The resulting oil was dissolved in ether (50ml) and treated with 4M hydrogen chloride in 1,4-dioxane (0.5ml). The precipitated solid was collected and dried *in vacuo* to give the title compound (0.09g).

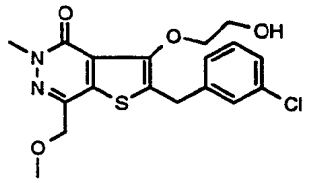
Melting point >230°C (dec)

MS (+ve APCI) 364 ($(M+H)^+$)

^{1}H NMR (DMSO d6) δ 0.90 (6H, d), 2.06-2.15 (1H, m), 2.58 (2H, d), 3.68 (3H, s), 4.66 (2H, d), 7.60 (1H, s), 7.78 (1H, t), 7.95 (1H, t), 8.14-8.20 (2H, m), 8.74 (1H, s), 9.18 (1H, s).

Example 45.

2-(3-Chlorophenyl)methyl-3-(2-hydroxyethoxy)-7-(methoxymethyl)-5-methylthieno[2,3-d]pyridazin-4(5H)-one



a) **Methyl 5-[(3-chlorophenyl)methyl]-4-hydroxythiophene-3-carboxylate**

Methyl 4-oxotetrahydrothiophene-3-carboxylate (18.5g) and 3-chlorobenzaldehyde (48.5g) were heated at 100°C with piperidine (4ml) for 15 minutes and then allowed to cool to room temperature. The resulting yellow solid was stirred in methanol (300ml) for 18 hours and collected. The yellow solid was suspended in ethanol (300ml) and dichloromethane (200ml), *para*-toluenesulfonic acid(10g) was added and the suspension was heated at reflux for 48 hours. The reaction mixture was allowed to cool and was then concentrated. The residue was purified by chromatography, eluting with 10:1 isohexane : dichloromethane, to give the sub-title compound (22.32g).

MS (+ve APCI) ($(M+H)^+$) 283/5

^{1}H NMR (DMSO d-6) δ 3.79 (3H, s), 4.08 (2H, s), 7.04 (1H, s), 7.33-7.39 (1H, m), 7.45-7.57 (2H, m), 7.65 (1H, s), 10.76 (1H, s).

b) **Methyl 5-[(3-chlorophenyl)methyl]-4-{2-[(1,1-dimethylethyl)dimethylsilyl]oxyethoxy}thiophene-3-carboxylate**

A mixture of methyl 5-[(3-chlorophenyl)methyl]-4-hydroxythiophene-3-carboxylate (11g), potassium carbonate (5.45g) and (2-bromoethoxy)(1,1-dimethylethyl)dimethylsilane (10g) was dissolved in acetone (250ml) and heated at reflux for 36 hours and then allowed to cool. The mixture was filtered, concentrated and purified by chromatography, eluting with 10:1 ethyl acetate : isohexane, to give the sub-title compound (8g).

MS (+ve APCI) ($(M+H)^+$) 442/4

c) **5-[(3-Chlorophenyl)methyl]-4-{2-[(1,1-dimethylethyl)dimethylsilyl]oxyethoxy}thiophene-3-carboxylic acid**

Methyl 5-[(3-chlorophenyl)methyl]-4-{2-[(1,1-dimethylethyl)dimethylsilyl]oxyethoxy}thiophene-3-carboxylate (10.2g) was dissolved in a mixture of 1M lithium hydroxide (50ml), methanol (50ml) and tetrahydrofuran (150ml) and stirred for 18hr. The reaction mixture was concentrated and the residue was partitioned between dichloromethane and 2M hydrochloric acid. The organic layer was collected, dried and filtered. t-Butyl-dimethylsilyl chloride (7g) and imidazole (3.1g) were added to the solution and the mixture was stirred for 72 hours. The reaction mixture was concentrated and the residue was dissolved in methanol. Potassium carbonate (5g) was added to the solution and the suspension was vigorously stirred for 3 minutes, then filtered and concentrated. The residue was dissolved in ethyl acetate, washed with 2M hydrochloric acid, dried, filtered and concentrated. The residue was purified by chromatography, eluting with 10:1:1 isohexane : ethyl acetate : acetic acid, to give the sub-title compound (4.2g).

MS (-ve APCI) ($(M-Me)^-$) 427/9

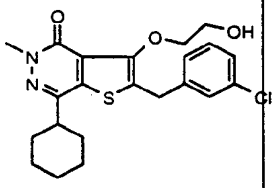
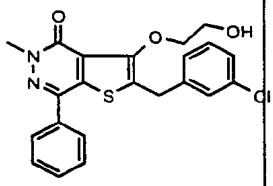
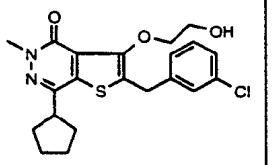
d) 2-[(3-Chlorophenyl)methyl]-3-(2-hydroxyethoxy)-7-(methoxymethyl)-5-methylthieno[2,3-d]pyridazin-4(5H)-one

2.0M butyl lithium in hexanes (1ml) was diluted with tetrahydrofuran (3ml) and cooled to -20°C. 5-[(3-Chlorophenyl)methyl]-4-{2-[(1,1-dimethylethyl)-dimethylsilyl]oxyethoxy}thiophene-3-carboxylic acid in tetrahydrofuran (1ml of 1M solution) was added slowly. The solution was mixed for 10 minutes and then 1mmol of 2,*N*-Dimethoxy-*N*-methylacetamide in 1ml of tetrahydrofuran was added. The solution was mixed for 10 minutes and was then added to 5ml of ammonium chloride solution. The reaction mixture was evaporated in air for 18 hours. The residue was dissolved in dichloromethane and washed with water twice. The solvent was allowed to evaporate and the residue was then dissolved in 5ml of ethanol. To this solution was added 92mg of methyl hydrazine. The resulting solution was heated at reflux for 4 hours. The reaction mixture was allowed to cool and the solvent was evaporated. Purification by column chromatography, eluting with an isohexane : ethyl acetate gradient, gave the title compound (4mg).

MS(+ve APCI) 395/397 (M+H)

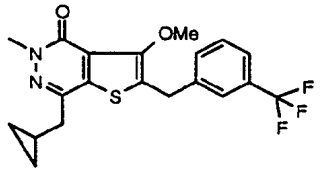
^{1}H NMR (DMSO d-6) δ 3.33 (3H, s), 3.76 (3H, s), 3.80-3.84 (2H, br), 4.12 (2H, s), 4.13-4.16 (2H, m), 4.48 (2H, s), 7.07-7.98 (4H, m).

The following compounds were made following the method of Example 44 using the appropriate *N,O*-dimethylhydroxylamide.

Example	Name	MS (+ve APCI) ((M+H)$^+$)	^{1}H NMR (DMSO d-6) δ
46 	2-[(3-Chlorophenyl)-methyl]-7-cyclohexyl-3-(2-hydroxyethoxy)-5-methylthieno[2,3-d]pyridazin-4(5H)-one	433/435	1.19-1.88 (10H, m), 2.52-2.62 (1H, m), 3.74 (3H, s), 3.82 (2H, bs), 4.11 (2H, s), 4.14-4.17 (2H, m), 7.06-7.09 (4H, m)
47 	2-[(3-Chlorophenyl)-methyl]-3-(2-hydroxyethoxy)-5-methyl-7-phenylthieno[2,3-d]pyridazin-4(5H)-one	427/429	3.86 (3H, s),2.82-2.86 (2H, m), 4.13 (2H, s), 4.18-4.21 (2H, m), 7.14-7.17 (2H, m), 7.40-7.43 (4H, m), 7.67-7.71 (3H, m)
48 	2-[(3-Chlorophenyl)-methyl]-7-cyclopentyl-3-(2-hydroxyethoxy)-5-methylthieno[2,3-d]pyridazin-4(5H)-one	419/421	0.76-0.86 (4H, m), 1.73-1.86 (5H, m), 3.74 (3H, s), 3.02-3.13 (2H, m), 4.11 (2H, s), 4.13-4.18 (2H, m), 7.06-7.11 (4H, m)

Example 49

7-Cyclopropylmethyl-3-methoxy-5-methyl-2-[(3-trifluoromethylphenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one



a) **Butyl 5-[(3-trifluoromethylphenyl)methyl]-4-hydroxythiophene-3-carboxylate**

Methyl 4-oxotetrahydrothiophene-3-carboxylate (3.2g) and 3-trifluoromethylbenzaldehyde (10.6g) were heated at 100°C with piperidine (170mg) for 15 minutes and then allowed to cool to room temperature. The resulting yellow solid was stirred in 150ml methanol for 18 hours and then collected. The yellow solid was suspended in butanol (150ml) with *para*-toluenesulfonic acid (10g) and heated at reflux for 48 hours. The reaction mixture was concentrated and chromatographed, eluting with 10:1 isohexane : dichloromethane, to give the sub-title compound (2.5g).

MS (+ve APCI) ($(M+H)^+$) 359

b) **Butyl 4-methoxy-2-[(3-trifluoromethylphenyl)methyl]-thiophene-3-carboxylate**

Butyl 5-[(3-trifluoromethylphenyl)methyl]-4-hydroxythiophene-3-carboxylate (2.5g) was dissolved in acetone (50ml). Potassium carbonate (1g) and methyl iodide (0.454ml) were added and the mixture was heated at reflux for 18 hours. The reaction mixture was allowed to cool and then concentrated. The residue was dissolved in ethyl acetate, washed with water, dried, filtered and evaporated. The residue was purified by chromatography, eluting with 40:1 isohexane : ethyl acetate, to give the sub-title compound (1.75g).

^{1}H NMR (DMSO d-6) δ 0.92 (3H, t), 1.34-1.47 (2H, m), 1.61-1.70 (2H, m), 3.72 (3H, s), 4.18 (2H, s), 4.21 (2H, d), 7.55-7.62 (4H, m), 8.10 (1H, s).

c) **4-Methoxy-5-[(3-trifluoromethylphenyl)methyl]thiophene-3-carboxylic acid**

Butyl 4-methoxy-2-[(3-trifluoromethylphenyl)methyl]thiophene-3-carboxylate (1.75g) was dissolved in a mixture of 1M lithium hydroxide (10ml), tetrahydrofuran (30ml) and methanol (10ml) and the solution was stirred for 18 hours. The reaction mixture was concentrated. The residue was redissolved in ethyl acetate and then washed 2M hydrochloric acid. The organic layer was dried and concentrated to give the sub-title compound as a white solid (1.25g).

MS (-ve APCI) ($(M-H)^-$) 315

^{1}H NMR (DMSO d-6) δ 3.71 (3H, s), 4.16 (2H, s), 7.54-7.61 (4H, m), 8.04 (1H, s), 12.64 (1H, s).

d) **2-(2-Cyclopropylacetyl)-4-methoxy-5-[(3-trifluoromethylphenyl)methyl]thiophene-3-carboxylic acid**

2M butyl lithium in hexanes (1.75ml) was added slowly to a solution of 4-methoxy-5-[(3-trifluoromethylphenyl)methyl]thiophene-3-carboxylic acid (500mg) in tetrahydrofuran (30ml) at -78°C. The resultant red solution was stirred for 20 minutes and then 2-cyclopropyl-*N*-methoxy-*N*-methylacetamide (229mg) in tetrahydrofuran (3ml) was added. The mixture was stirred for 20 minutes at -78°C and was then allowed to warm to room temperature. After 5 hours water was added and the mixture was extracted with ethyl acetate. The organic phase was dried and concentrated. Purification of the residue by chromatography, eluting with 10:10:1 isohexane : ether: acetic acid, gave the sub-title compound (177mg).

MS (+ve APCI) ($(M+H)^+$) 399

^{1}H NMR (DMSO d-6) δ 0.91-1.14 (2H, m), 0.44-0.49 (2H, m), 0.94-1.14 (1H, m), 2.66 (2H, d), 3.77 (3H, s), 4.26 (2H, s), 7.56-7.66 (3H, m), 7.69 (1H, s), 13.66 (1H, bs).

e) **7-Cyclopropylmethyl-3-methoxy-5-methyl-2-[(3-trifluoromethylphenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one**

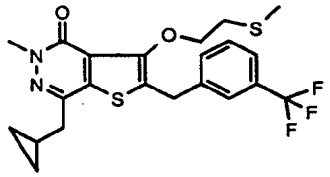
2-(2-Cyclopropylacetyl)-4-methoxy-5-[(3-trifluoromethylphenyl)methyl]thiophene-3-carboxylic acid (8.65g) was dissolved in 125ml of ethanol. To this solution was added methylhydrazine (2.34ml) and the mixture was heated at reflux for 18 hours. The reaction mixture was allowed to cool and then concentrated. The residue was partitioned between ethyl acetate and 2M hydrochloric acid. The organic layer was collected, dried, filtered and concentrated to give the title compound (8.8g).

MS (+ve APCI) ($(M+H)^+$) 409

^{1}H NMR (DMSO d-6) δ 0.22(2H, m), 0.48(2H, m), 1.00-1.10(1H, m), 2.61(2H, d), 3.69(3H, s), 3.88(3H, s), 4.33(2H, s), 7.55-7.64(3H, m), 7.69(1H, s).

Example 50.

7-Cyclopropylmethyl-5-methyl-3-[2-(methylthio)ethoxy]-2-[(3-trifluoromethylphenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one



a) **7-Cyclopropylmethyl-3-hydroxy-5-methyl-2-[(3-trifluoromethylphenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one**

7-Cyclopropylmethyl-3-methoxy-5-methyl-2-[(3-trifluoromethylphenyl)methyl]-thieno[2,3-d]pyridazin-4(5H)-one (8.8g) was dissolved in dichloromethane (250ml) and cooled to -15 °C. Boron tribromide in dichloromethane (1M, 24ml) was added. The reaction was allowed to warm to room temperature and left to stir for 72 hours. Water was added and the mixture was extracted with ethyl acetate. The ethyl acetate was dried, filtered and concentrated. The residue was purified by chromatography, eluting with 1:1 isohexane : ether, and then recrystallised from isohexane to give the sub-title compound (4.5g).

Melting point 92-93°C

MS (+ve APCI) ($(M+H)^+$) 395

^{1}H NMR (DMSO d-6) δ 0.21-0.23 (2H, m), 0.48-0.50 (2H, m), 1.04-1.08 (1H, m), 2.60 (2H, d), 3.67 (3H, s), 4.26 (2H, s), 7.56-7.64 (3H, m), 7.67 (1H, s), 9.27 (1H, s).

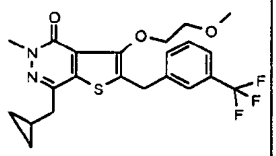
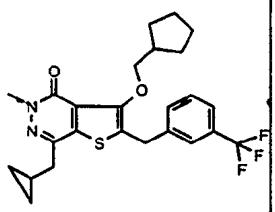
b) **7-Cyclopropylmethyl-5-methyl-3-[2-(methylthio)ethoxy]-2-[(3-trifluoromethylphenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one**

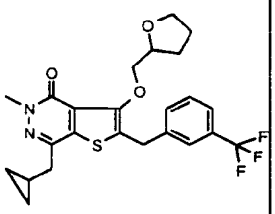
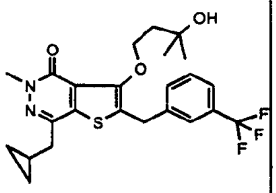
To 5ml of dry tetrahydrofuran was added 0.64ml of 1M triphenylphosphine in tetrahydrofuran followed by 0.64ml of 1M diethyl diazodicarboxylate in tetrahydrofuran and then by 0.64ml of 1M 2,6-di-*t*-butylphenol in tetrahydrofuran. This mixture was mixed for 5 minutes and then 1.28ml of 0.5M 2-(methylthio)ethanol in tetrahydrofuran was added. The solution was then mixed for 5 minutes. 7-Cyclopropylmethyl-3-hydroxy-5-methyl-2-[(3-trifluoromethylphenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one (248mg in 1ml tetrahydrofuran) was added and the solution was mixed periodically over 24 hours. The solution was opened to the air for 18 hours and then purified by chromatography, eluting with an isohexane ethyl acetate gradient, to give the title compound (77mg).

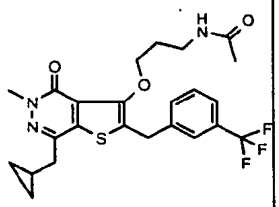
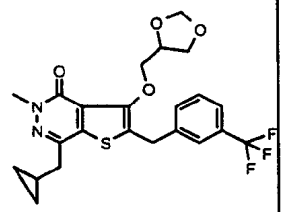
MS (ES+ve, TOF) ($(M+H)^+$) found : 469.1241; theory : 469.1231

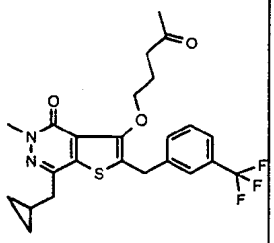
^{1}H NMR (DMSO d-6) δ 0.21-0.23 (2H, m), 0.48-0/50 (2H, m), 1.02-1.08 (1H, m), 2.11 (3H, s), 2.66 (2H, d), 2.85 (2H, t), 3.69 (3H, s), 4.30 (2H, t), 4.40 (2H, s), 7.56-7.64 (3H, m), 7.72 (1H, s).

The following examples were prepared following the method of Example 50 using the appropriate alcohol as reactant.

Example	Name	MS (ES+ve, TOF) ($(M+H)^+$)	^{1}H NMR (DMSO d-6) δ
51 	7-Cyclopropyl-methyl-3-(2-methoxyethoxy)-5-methyl-2-[(3-trifluoromethyl-phenyl)methyl]-thieno[2,3-d]-pyridazin-4(5H)-one.	found : 453.1442 theory: 453.1459	0.21-0.23 (2H, m), 0.47-0.49 (2H, m), 1.01-1.05 (1H, m), 2.61 (2H, d), 3.30 (3H, s), 3.59-3.62 (2H, m), 3.68 (3H, s), 4.31-4.32 (2H, m), 4.36 (2H, s), 7.55-7.63 (3H, m), 7.71 (1H, s)
52 	3-Cyclopentyl-methoxy-7-cyclopropylmethyl-5-methyl-2-[(3-trifluoromethyl-phenyl)methyl]-thieno[2,3-d]-pyridazin-4(5H)-one.	found : 477.1835 theory : 477.1823	0.21-0.24 (2H, m), 0.47-0.50 (2H, m), 1.02-1.04 (1H, m), 1.33-1.35 (2H, m), 1.53-1.55 (4H, m), 1.73-1.77 (2H, m), 2.31-2.33 (1H, m), 2.61(2H, d), 3.68 (3H, s), 3.97 (2H, d), 4.34 (2H, s), 7.55-7.63 (3H, m), 7.69 (1H, s)

Example	Name	MS (ES+ve, TOF) ($(M+H)^+$)	^{1}H NMR (DMSO d-6) δ
53 	7-Cyclopropylmethyl-5-methyl-3-(tetrahydrofuran-2-ylmethoxy)-2-[(3-trifluoromethyl-phenyl)methyl]-thieno[2,3-d]-pyridazin-4(5H)-one	found : 479.1701 theory :479.1616	0.22-0.26 (2H, m), 0.45-0.49 (2H, m), 1.01-1.03 (H, m), 1.60-1.70 (1H, m), 1.80-1.90 (2H, m), 1.91-1.99 (1H, m), 2.60 (2H, d),3.45 (3H, s), 3.60-3.70 (1H, m), 3.70-3.79 (1H, m), 4.01-4.09 (1H, m), 4.11-4.19 (1H, m), 4.18-4.26 (1H, m), 4.37 (2H, d), 7.55-7.65 (3H, m), 7.71 (1H, s)
54 	7-Cyclopropylmethyl-3-(3-hydroxy-3-methyl-butoxy)-5-methyl-2-[(3-trifluoromethyl-phenyl)methyl]-thieno[2,3-d]-pyridazin-4(5H)-one	found : 481.1762 theory : 481.1772	0.21-0.23 (2H, m), 0.47-0.49 (2H, m), 1.02-1.06 (1H, m), 1.06 (6H, s), 1.86 (2H, t), 2.62 (2H, d), 3.68 (3H, s), 4.20 (2H, t), 4.32 (1H, s), 4.33 (2H, s), 7.53-7.57 (3H, m), 7.68 (1H, s)

Example	Name	MS (ES+ve, TOF) ($(M+H)^+$)	^{1}H NMR (DMSO d-6) δ
55 	N-{3-[7-Cyclopropylmethyl-5-methyl-4-oxo-2-[(3-trifluoromethyl-phenyl)methyl]-4,5-dihydrothieno-[2,3-d]pyridazin-3-yl]oxypropyl}-acetamide.	found : 494.1731 theory : 494.1725	0.19-0.21 (2H, m), 0.46-0.48 (2H, m), 1.02-1.04 (1H, m), 1.80(3H, s), 1.85-1.89 (2H, m), 2.63(2H, d), 3.23-3.27 (2H, m), 3.69 (3H, s), 4.09 (2H, t), 4.34 (2H, s), 6.34 (1H, s), 7.57-7.63 (3H, m), 7.95 (1H, s)
56 	7-Cyclopropylmethyl-3-([1,3]dioxolan-4-ylmethoxy)-5-methyl-2-[(3-trifluoromethyl-phenyl)methyl]-thieno[2,3-d]-pyridazin-4(5H)-one	found : 481.1416 theory : 481.1409	0.19-0.21 (2H, m), 0.45-0.47 (2H, m), 1.04-1.08 (1H, m), 2.61 (2H, d), 3.67 (3H, d), 3.74-4.25 (2H, dm), 4.01 (2H, d), 4.36-4.42 (2H, d), 4.56 (1H, t), 4.79-4.99 (2H, dm), 7.57-7.64 (3H, m), 7.71-7.85 (1H, m)

Example	Name	MS (ES+ve, TOF) ($(M+H)^+$)	^{1}H NMR (DMSO d-6) δ
57 	7-Cyclopropylmethyl -5-methyl -3-(4-oxopentyl)oxy-2-[(3-trifluoromethyl-phenyl)methyl]-thieno[2,3-d]-pyridazin-4(5H)-one	found : 479.1631 theory : 479.1616	0.23-0.27 (2H, m), 0.52-0.56 (2H, m), 1.07-1.11 (1H, m), 2.09-2.11 (2H, m), 2.19 (3H, s), 2.63 (2H, d), 2.76 (2H, t), 3.81 (3H, s),4.17 (2H, t), 4.22 (2H, s), 7.42-7.44 (2H, m), 7.51-7.53 (2H, m)

Pharmacological Data

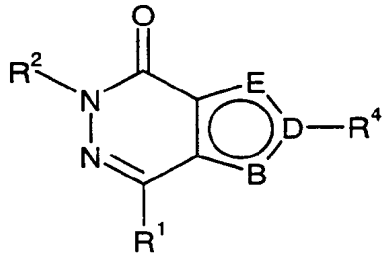
Inhibition of Human Mixed Lymphocyte Reaction (MLR)

The MLR test was performed in 96-well flat bottomed microtitre plates. Compounds were prepared as 10 mM stock solution in dimethyl sulfoxide. A 50 fold dilution of this was prepared in a RPMI 1640 medium cell culture solution. Serial dilutions were prepared from this solution. 10 µl of the 50 fold diluted stock, or dilutions of it, were added to the wells to give concentrations in the assay starting at 9.5µm and decreasing. Into each well was placed 1.5 x 10^5 cells from each of two responding donors in a final volume of 0.2 ml RPMI 1640 medium supplemented with 10% human serum, 2 mM L-glutamine and penicillin/streptomycin. The cells were incubated at 37 °C in a humidified atmosphere at 5% carbon dioxide for 120 hours. ^{3}H-Thymidine (0·5 µCi) was added for the final 6 hours of the incubation. The level of radioactivity incorporated by the cells was then determined, which is a measure of T-cell proliferation.

The title compounds of Examples 1 to 57 were found to exhibit an IA_{50} value of less than 1 x 10^{-6} M in the above test.

CLAIMS

1. A compound of general formula



(I)

wherein B represents a group CH or a nitrogen (N), sulfur (S) or oxygen (O) atom; D represents a carbon (C) or nitrogen (N) atom; E represents a group CR^3 or a nitrogen (N) atom; when D is a carbon atom, then B is a sulfur or oxygen atom and E is a group CR^3, and when D is a nitrogen atom, then either B is a group CH and E is a group CR^3 or a nitrogen atom, or B is a nitrogen atom and E is a group CR^3; R^1 represents a group NR'R'' where R' represent a hydrogen atom or a C_1-C_6 alkyl group, R'' represents a C_1-C_6 alkyl group, or R' and R'' together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated heterocyclic ring, or R^1 represents a C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_3-alkyloxyC_1-C_3-alkyl, C_3-C_6-cycloalkyloxyC_1-C_3-alkyl, C_3-C_6 alkenyl, phenyl, C_3-C_7 cycloalkyl, C_3-C_5 cycloalkylmethyl or C_3-C_7 cycloalkenyl group, each of which may be optionally substituted by one or more halogen atoms; R^2 represents a methyl group, or a C_2-C_6 alkyl group optionally substituted by a C_1-C_6 alkoxy group other than in the 1-position; R^3 represents a hydrogen atom or a group X-R^5 or X-Ar^1; X represents a group -O-, $S(O)_n$, $SO_2N(R^6)$ or $C(=O)N(R^6)$; n is 0, 1 or 2; R^5 represents an optionally substituted alkyl or alkenyl group, or, additionally, in the case where X represents $SO_2N(R^6)$ or $C(=O)N(R^6)$, R^5 and R^6 together with the nitrogen atom to which they are attached may form an optionally substituted 3- to 7-membered heterocyclic ring; Ar^1 represents an optionally substituted phenyl or pyridyl group; R^6 represents a hydrogen atom, C_1-C_6 alkyl or is linked to R^5 as defined above; R^4 represents a group CHR^7Ar^2 or Ar^3 or, additionally, in the case where D represents a carbon atom, a group $C(O)Ar^2$ or $CR^7(OH)Ar^2$; Ar^2 represents an aryl or heteroaryl group which may be optionally substituted; Ar^3 represents an acenaphthenyl, indanyl or fluorenyl group, each of which

may be optionally substituted; and R^7 represents a hydrogen atom or a C_1-C_4 alkyl group; or a pharmaceutically-acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein R^1 represents a C_1-C_4 alkylamino group, or R^1 represents a C_3-C_5 alkyl, C_1-C_4 alkoxy, C_1-C_3-alkyloxyC_1-C_3-alkyl, C_3-C_6-cycloalkyloxyC_1-C_3-alkyl, C_3-C_6 alkenyl, phenyl, C_3-C_5 cycloalkyl, C_3-C_5 cycloalkylmethyl or C_3-C_5 cycloalkenyl group, each of which may be optionally substituted by one to four halogen atoms.

3. A compound according to claim 1 or claim 2, wherein R^2 represents a methyl group, or a C_2-C_6 alkyl group optionally substituted by a C_1-C_4 alkoxy group other than in the 1-position.

4. A compound according to any one of the preceding claims, wherein R^4 represents a group CHR^7Ar^2, $C(O)Ar^2$ or $CR^7(OH)Ar^2$.

5. A compound according to claim 4, wherein Ar^2 represents a phenyl, naphthyl, pyridyl, quinolinyl, isoquinolinyl, naphthyridinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, thienyl, benzothienyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl, indolyl, indolizinyl, pyrazolyl, indazyl, imidazolyl, benzimidazolyl, imidazopyridyl, triazolyl, benzotriazolyl or triazolopyridyl group, each of which may be optionally substituted by one or more substituent groups independently selected from halogen, trifluoromethyl, trifluoromethoxy, amino, cyano, carboxyl, nitro, C_1-C_6 alkyl, C_1-C_6 alkoxy, (di)C_1-C_6 alkylamino, C_2-C_6 acylamino, C_1-C_6 alkylsulfonamido, CONH-(C_1-C_6 alkyl) and C_1-C_6 alkoxycarbonyl.

6. A compound according to any one of the preceding claims, wherein X represents a group -O-, $S(O)_n$ where n is 0, 1 or 2, or a group $C(=O)N(R^6)$.

7. A compound according any one of the preceding claims, wherein R^5 represents a C_2-C_6 alkyl or C_2-C_6 alkenyl group optionally substituted by one or more substituent groups independently selected from amido, amino, carboxyl, cyano, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, C_3-C_7 cycloalkyl, (di) C_1-C_6 alkylamino, C_2-C_6 acylamino, C_1-C_6 alkylsulfonamido, tetrahydrofuranyl, dioxolanyl, imidazolyl, haloC_1-C_6alkylsulfonamido and tetrazolyl.

8. A compound according to any one of claims 1 to 6, wherein Ar^1 represents a phenyl or pyridyl group optionally substituted by one or more substituent groups independently selected from carboxyl, hydroxyl, C_2-C_6 acylamino, C_1-C_6 alkylamido, C_1-C_6 alkylsulfonamido and (di)C_1-C_6 alkylsulfamoyl.

9. A compound according to claim 1 being:

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one,

2,6-Dihydro-2-(2-methoxyethyl)-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one,

2,6-Dihydro-7-[(3-hydroxypropyl)thio]-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one,

4-{[2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1-oxo-1*H*-pyrrolo[3,4-*d*]pyridazin-7-yl]thio}butanoic acid,

2,6-Dihydro-7-[(3-hydroxypropyl)sulfinyl]-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one,

2,6-Dihydro-7-[(3-hydroxypropyl)sulfonyl]-2-methyl-4-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1*H*-pyrrolo[3,4-*d*]pyridazin-1-one,

2-[1-Hydroxy-1-(1-naphthalenyl)methyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-*d*]pyridazin-4(5*H*)-one,

5-Methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)thieno[2,3-*d*]pyridazin-4(5*H*)-one,

3-[(3-Hydroxypropyl)thio]-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-thieno[2,3-*d*]pyridazin-4(5*H*)-one,

5-Methyl-7-(2-methylpropyl)-2-(1-naphthalenylcarbonyl)thieno[2,3-d]pyridazin-4(5H)-one,

3-[(3-Hydroxypropyl)sulfinyl]-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)thieno[2,3-d]pyridazin-4(5H)-one,

4-{[4,5-Dihydro-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4-oxothieno[2,3-d]pyridazin-3-yl]thio}butanoic acid,

5-Methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-3-(2-pyridinylthio)thieno[2,3-d]pyridazin-4(5H)-one,

3-[(3-Hydroxypropyl)sulfonyl]-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)thieno[2,3-d]pyridazin-4(5H)-one,

2-[1-Hydroxy-1-phenylmethyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one,

5-Methyl-7-(2-methylpropyl)-2-phenylmethylthieno[2,3-d]pyridazin-4(5H)-one,

3-[(3-Hydroxypropyl)thio]-5-methyl-7-(2-methylpropyl)-2-phenylmethylthieno[2,3-d]pyridazin-4(5H)-one,

3-[(3-Hydroxypropyl)sulfonyl]-5-methyl-7-(2-methylpropyl)-2-phenylmethylthieno-[2,3-d]pyridazin-4(5H)-one,

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-phenylmethyl-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-phenylmethyl-7-(2-pyridinylthio)-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-7-[(3-hydroxypropyl)thio]-2-methyl-4-(2-methylpropyl)-6-phenylmethyl-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(3,4,5-trimethoxyphenyl)methyl-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-2-methyl-6-(1-naphthalenylmethyl)-4-(1-methylethyl)amino-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(4-pyridinyl)methyl-1H-pyrrolo[3,4-d]pyridazin-1-one,

6-(2-Chlorophenyl)methyl-2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one,

6-(3,5-Difluorophenyl)methyl-2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one,

6-(2-Chloro-6-fluorophenyl)methyl-2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one,

6-(3-Chloro-2-fluorophenyl)methyl-2,6-dihydro-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(2-quinolinylmethyl)-1H-pyrrolo[3,4-d]-pyridazin-1-one,

2,6-Dihydro-2-methyl-4-(2-methylpropyl)-6-(2-trifluoromethylphenyl)methyl-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-6-(2-imidazo[1,2-a]pyridinyl)methyl-2-methyl-4-(2-methylpropyl)-1H-pyrrolo[3,4-d]pyridazin-1-one,

2,6-Dihydro-N-[3-(1-1H-imidazolyl)propyl]-2-methyl-4-(2-methylpropyl)-1-oxo-6-phenylmethyl-1H-pyrrolo[3,4-d]pyridazin-1-one-5-carboxamide,

2,5-Dihydro-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4H-pyrazolo[3,4-d]pyridazin-4-one,

2,6-Dihydro-6-methyl-4-(2-methylpropyl)-2-(1-naphthalenylmethyl)-7H-pyrazolo[3,4-d]pyridazin-7-one,

2,5-Dihydro-3-[(3-hydoxypropyl)thio]-5-methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)-4H-pyrazolo[3,4-d]pyridazin-4-one,

2-[1-Hydroxy-1-(1-naphthalenyl)methyl]-5-methyl-7-(2-methylpropyl)furo[2,3-d]pyridazin-4(5H)one,

5-Methyl-7-(2-methylpropyl)-2-(1-naphthalenylmethyl)furo[2,3-d]pyridazin-4(5H)one,

2-[1-Hydroxy-1-(3-cyanophenyl)methyl]-5-methyl-7-(2-methylpropyl)furo[2,3-d]pyridazin-4(5H)one,

2-(3-Cyanophenyl)methyl-5-methyl-7-(2-methylpropyl)furo[2,3-d]pyridazin-4(5H)one,

2-(2-Trifluoromethylphenyl)methyl-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one,

2-[(1-Hydroxy-1-pyridin-3-yl)methyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one hydrochloride,

5-Methyl-7-(2-methylpropyl)-2-(3-pyridinylmethyl)thieno[2,3-d]pyridazin-4(5H)-one,

2-(2-Chloro-6-fluorophenyl)methyl-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one,

2-[(1-Hydroxy-1-quinolin-3-yl)methyl]-5-methyl-7-(2-methylpropyl)thieno[2,3-d]pyridazin-4(5H)-one,

5-Methyl-7-(2-methylpropyl)-2-(3-quinolinylmethyl)thieno[2,3-d]pyridazin-4(5H)-one hydrochloride,

2-(3-Chlorophenyl)methyl-3-(2-hydroxyethoxy)-7-(methoxymethyl)-5-methylthieno[2,3-d]pyridazin-4(5H)-one,

2-[(3-Chlorophenyl)methyl]-7-cyclohexyl-3-(2-hydroxyethoxy)-5-methylthieno[2,3-d]pyridazin-4(5H)-one,

2-[(3-Chlorophenyl)methyl]-3-(2-hydroxyethoxy)-5-methyl-7-phenylthieno[2,3-d]pyridazin-4(5H)-one,

2-[(3-Chlorophenyl)methyl]-7-cyclopentyl-3-(2-hydroxyethoxy)-5-methylthieno[2,3-d]pyridazin-4(5H)-one,

7-Cyclopropylmethyl-3-methoxy-5-methyl-2-[(3-trifluoromethylphenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one,

7-Cyclopropylmethyl-5-methyl-3-[2-(methylthio)ethoxy]-2-[(3-trifluoromethylphenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one,

7-Cyclopropylmethyl-3-(2-methoxyethoxy)-5-methyl-2-[(3-trifluoromethylphenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one,

3-Cyclopentylmethoxy-7-cyclopropylmethyl-5-methyl-2-[(3-trifluoromethylphenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one,

7-Cyclopropylmethyl-5-methyl-3-(tetrahydrofuran-2-ylmethoxy)-2-[(3-trifluoromethylphenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one,

7-Cyclopropylmethyl-3-(3-hydroxy-3-methyl-butoxy)-5-methyl-2-[(3-trifluoromethyl-phenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one,

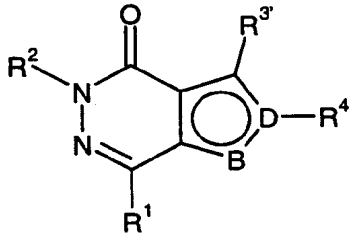
N-{3-[7-Cyclopropylmethyl-5-methyl-4-oxo-2-[(3-trifluoromethylphenyl)methyl]-4,5-dihydrothieno[2,3-d]pyridazin-3-yl]oxypropyl}acetamide,

7-Cyclopropylmethyl-3-([1,3]dioxolan-4-ylmethoxy)-5-methyl-2-[(3-trifluoromethyl-phenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one, or

7-Cyclopropylmethyl-5-methyl -3-(4-oxopentyl)oxy-2-[(3-trifluoromethyl-phenyl)methyl]thieno[2,3-d]pyridazin-4(5H)-one.

10. A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises:

(a) when X represents $S(O)_n$ and n is 1 or 2, oxidising a compound of general formula

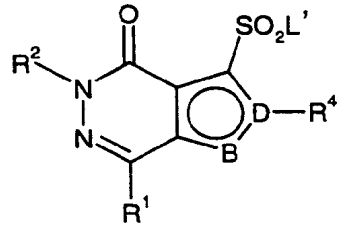


(II)

wherein $R^{3'}$ represents $S\text{-}R^5$ or $S\text{-}Ar^1$ and B, D, R^1, R^2, R^4, R^5 and Ar^1 are as defined in claim 1; or

(b) when X represents $S(O)_n$ and n is 0, reacting a corresponding compound of formula (I) in which E is CR^3 and R^3 is a hydrogen atom, with a compound of general formula (III), $R^8\text{-}S\text{-}S\text{-}R^8$, wherein the groups R^8 both represent R^5 or Ar^1 as defined in claim 1, or with a compound of general formula (IV), $L\text{-}S\text{-}R^8$, wherein L represents a leaving group and R^8 is as hereinbefore defined; or

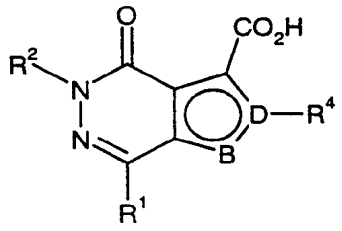
(c) when X represents $SO_2N(R^6)$, reacting a compound of general formula



(V)

wherein L' represents a leaving group and B, D, R^1, R^2 and R^4 are as defined in claim 1, with a compound of general formula (VI), HNR^6R^8, wherein R^6 is as defined in claim 1 and R^8 is as defined in (b) above; or

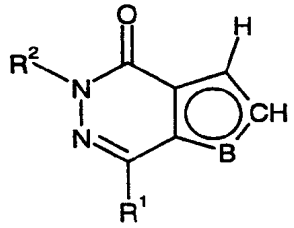
(d) when X represents $C(=O)N(R^6)$, reacting a compound of general formula



(VII)

wherein B, D, R^1, R^2 and R^4 are as defined in claim 1 with a compound of formula (VI) as defined in (c) above; or

(e) when D is a carbon atom, E is CR^3 , R^3 is a hydrogen atom and R^4 is $CH(OH)Ar^2$, reacting a compound of general formula



(VIII)

wherein B, R^1 and R^2 are as defined in claim 1, with a compound of general formula (IX), Ar^2CHO, where Ar^2 is as defined in claim 1; or

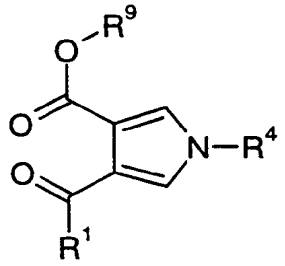
(f) when D is a carbon atom, E is CR^3, R^3 is a hydrogen atom and R^4 is CHR^7Ar^2, reducing a corresponding compound of formula (I) in which R^4 is $CR^7(OH)Ar^2$; or

(g) when D is a carbon atom, E is CR^3, R^3 is a hydrogen atom and R^4 is $C(O)Ar^2$, oxidising a corresponding compound of formula (I) in which R^4 is $CH(OH)Ar^2$; or

(h) when D is a carbon atom, E is CR^3, R^3 is a hydrogen atom, R^4 is $CR^7(OH)Ar^2$ and R^7 is a C_1-C_4 alkyl group, reacting a corresponding compound of formula (I) in which R^4 is $C(O)Ar^2$, with a C_1-C_4 alkylating agent; or

(i) when D is a carbon atom, E is CR^3, R^3 is a hydrogen atom and R^4 is Ar^3, reacting a compound of formula (VIII) as defined in (e) above, with 1-indanone, 2-indanone, 9-fluoreneone or 1-acenaphthenone, followed by a reduction reaction; or

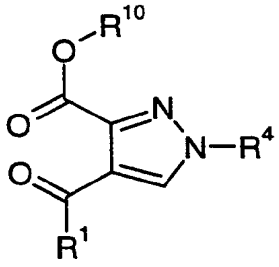
(j) when D is a nitrogen atom, B is CH, E is CR^3 and R^3 is a hydrogen atom, reacting a compound of general formula



(X)

wherein R^9 is an alkyl group and R^1 and R^4 are as defined in claim 1, with a compound of general formula (XI), R^2NHNH_2, wherein R^2 is as defined in claim 1; or

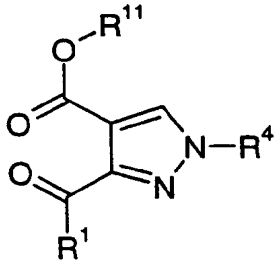
(k) when D is a nitrogen atom, B is CH and E is a nitrogen atom, reacting a compound of general formula



(XII)

wherein R^{10} is an alkyl group and R^1 and R^4 are as defined in claim 1, with a compound of formula (XI) as defined in (j) above;

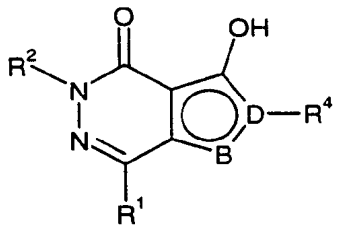
(l) when D is a nitrogen atom, B is a nitrogen atom, E is CR^3 and R^3 is a hydrogen atom, reacting a compound of general formula



(XIII)

wherein R^{11} is an alkyl group and R^1 and R^4 are as defined in claim 1, with a compound of formula (XI) as defined in (j) above;

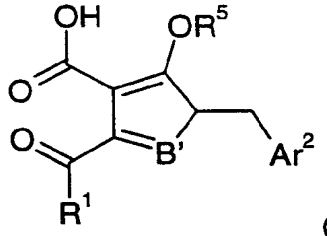
(m) when X is -O-, reacting a compound of general formula



(XIIIA)

wherein B, D, R^1, R^2 and R^4 are as defined in claim 1, with a compound of general formula (XIIIB), R^8-L'', wherein L'' represents a leaving group such as a halogen atom and R^8 is as defined in (b) above; or

(n) when D is a carbon atom, B is a sulfur or oxygen atom, R^3 represents -OR^5 and R^4 represents CH_2Ar^2, reacting a compound of general formula



(XIIIC)

wherein B' represents asulfur or oxygen atom and R^1, R^5 and Ar^2 are as defined in claim 1, with a compound of formula (XI) as defined in (j) above;

and optionally thereafter converting the compound of formula (I) to a further compound of formula (I) and/or forming a pharmaceutically-acceptable salt or solvate of the compound of formula (I).

11. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 in association with a pharmaceutically-acceptable adjuvant, diluent or carrier.

12. A process for the preparation of a pharmaceutical composition as claimed in claim 11 which comprises mixing a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as defined in any one of claims 1 to 9 with a pharmaceutically-acceptable adjuvant, diluent or carrier.

13. A compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 for use in therapy.

14. Use of a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in therapy.

15. A method of effecting immunosuppression which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9.

16. A method of treating, or reducing the risk of, a reversible obstructive airways disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/02191

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 487/04, C07D 495/04, C07D 491/04, A61K 31/50, A61K 31/40, A61K 31/38, A61K 31/34, A61K 31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9112251 A1 (CHUGAI SEIYAKU KABUSHIKI KAISHA), 22 August 1991 (22.08.91) --	1-16
X	Chem. Pharm. Bull., Volume 43, No 2, 1995, Masahisa Yamaguchi et al, "Novel Antiasthmatic Agents with Dual Activities of Thromboxane A2Synthetase Inhibition and Bronchodilation. V.1) Thienopyridazione Derivatives", page 236 - page 240, page 237, numbers 11a,b,12a,b --	1-16
X	FR 2478640 A1 (SANOFI), 25 Sept 1981 (25.09.81), the claims, formula I; page 19 --	1-16

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 March 1999	17 -03- 1999
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/02191

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0475527 A2 (STERLING DRUG INC.), 18 March 1992 (18.03.92), page 69, line 9; page 76, line 36 - line 48	1-10
	--	
A	EP 0534443 A1 (MITSUBISHI KASEI CORPORATION), 31 March 1993 (31.03.93), page 78, number XXI; page 84, line 39	1-10
	--	
A	FR 1453897 B1 (M. MAX FERNAND ROBBA), 22 August 1966 (22.08.66), page 2; page 3; page 7, examples 16-18; page 8, no VII; page 9, examples 26-35	1-10
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/02191

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 15, 16
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 15, 16 relate to methods of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/02/99

International application No.
PCT/SE 98/02191

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9112251 A1	22/08/91	AU 7238191 A	03/09/91
FR 2478640 A1	25/09/81	NONE	
EP 0475527 A2	18/03/92	AT 163413 T	15/03/98
		AU 639821 B	05/08/93
		AU 649919 B	02/06/94
		AU 3706993 A	29/07/93
		AU 8264191 A	12/03/92
		CA 2050962 A	11/03/92
		DE 69128949 D	00/00/00
		FI 914258 A	11/03/92
		HU 64313 A	28/12/93
		HU 211316 B	28/11/95
		HU 9500634 A	28/11/95
		IL 99452 A	05/12/96
		IL 113677 A	10/06/97
		JP 5339246 A	21/12/93
		NO 300268 B	05/05/97
		NO 952465 A	20/06/95
		NZ 239407 A	27/06/94
		NZ 248974 A	26/05/97
		NZ 264710 A	26/05/97
		NZ 280544 A	26/05/97
		PT 98918 A	31/07/92
		US 5380721 A	10/01/95
		US 5624922 A	29/04/97
EP 0534443 A1	31/03/93	AT 175200 T	15/01/99
		CA 2078699 A	27/03/93
		JP 2730421 B	25/03/98
		JP 6135938 A	17/05/94
		US 5324727 A	28/06/94
		US 5462941 A	31/10/95
FR 1453897 B1	22/08/66	NONE	